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SIZE ANALYSIS OF WATER AEROSOLS

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SIZE ANALYSIS of water aerosols is difficult because water droplets evaporate quickly in room air. For this reason most methods of size analysis are indirect, in the sense that water droplets are allowed to hit a suitably prepared surface, where they leave a permanent imprint. However, evaporation may occur before the droplets reach the sampling surface, and only the largest droplets may carry sufficient momentum to penetrate it. Moreover, a round droplet is smaller than the flat imprint that it leaves on the sampling surface. Therefore a calibration factor must be determined, to convert the measured diameter of the flat imprint into the diameter of the round droplet that originally made the imprint.

The problem thus resolves itself into a search for a suitable water-sensitive sampling surface; determination of sampling conditions that will preclude evaporation of the aerosol and insure that a representative sample of droplets leaves imprints on the sampling slide; and calibration of the procedure to permit evaluation of the original spherical droplet diameters.

In the present paper, four different methods of droplet-sizing for water aerosols are evaluated. One of these has been calibrated by an absolute method, and calibration factors for the other methods have been derived by comparison. Work with salt solutions and with nonvolatile liquids is of interest for comparative purposes, and two further methods for use with non-volatile liquids are described.

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RATE OF EVAPORATION OF WATER DROPLETS

Appreciation of the rapid rate at which water droplets evaporate in room air is an essential prerequisite to an attack on the problem of sampling such droplets. Tables I and II present data recalculated from

TABLE I. CALCULATED MASS RATE OF EVAPORATION OF ISOLATED WATER DROPLETS IN AIR OF 100% HUMIDITY AT 0 OR 21 C AND 760 mm PRESSURE

Droplet Diameter μ	Mass at 0 C Gm.	Percentage of Mass Evaporated in 1 Second	
		at 0 C	at 21 C
100	5.24×10^{-7}	0.00033	0.0011
50	6.54×10^{-8}	0.0026	0.0092
20	4.19×10^{-9}	0.041	0.14
10	5.24×10^{-10}	0.33	1.1
5	6.54×10^{-11}	2.6	9.2
2	4.19×10^{-12}	41	(140)
1	5.24×10^{-13}	(330)	(1,100)

the classical equations relating the rate of evaporation of an isolated droplet with parameters such as the excess vapor pressure of a spherical surface and the diffusion coefficient of water vapor.[3,4,6,7]

Table I shows that the rate of evaporation is fast even at 100 per cent saturation, and decreases rapidly with increase in droplet size. Table II

TABLE II. CALCULATION OF EVAPORATION TIMES OF ISOLATED WATER DROPLETS IN AIR OF DIFFERENT HUMIDITIES AT 21 C AND 760 mm PRESSURE

Diameter of Water Droplet μ	Time for Complete Evaporation at Relative Humidities of				
	100%	99%	90%	50%	0%
	Seconds	Seconds	Seconds	Seconds	Seconds
100	129,000	280	28	5.6	2.8
50	16,200	69	6.9	1.38	0.69
20	1,040	11.1	1.11	0.22	0.111
10	129	2.8	0.28	0.056	0.028
5	16.2	0.69	0.069	0.0138	0.0069
2	1.04	0.111	0.0111	0.0022	0.00111
1	0.129	0.028	0.0028	0.00056	0.00028

demonstrates that the major change in rate of evaporation occurs between 90 and 100 per cent humidity. Since the rate drops sharply as 100 per cent saturation is approached, it is reasonable to suppose that condensation onto the droplets should occur under certain conditions of super saturation and that at some intermediate degree of supersaturation an equilibrium should be found at which isloated droplets will neither evaporate nor grow in size. Table III gives this equilibrium supersaturation as calculated by the Kelvin equation, which relates the excess vapor pressure of a spherical droplet with its surface tension[3,4,6,7] and applies without correction only in the absence of electrical charge or dissolved substances.

It is seen that only slight supersaturation is required to hold isolated water droplets in equilibrium with their surroundings.

Table III gives figures that help to bridge the gap between an isolated droplet and an aerosol, which may contain billions of such droplets. The isolated droplet is surrounded by an atmosphere at ambient saturation and will evaporate at the rates given in Tables I and II. A cloud of aerosol droplets, on the other hand, at the instant of formation may contain individual droplets evaporating at the rates given by Tables I and II; from this instant onwards, the vapor pressure of the atmosphere within the aerosol will rise, while the rate of evaporation of the droplets will decrease asymptotically as the equilibrium saturation is approached within

TABLE III. PER CENT SUPERSATURATION OF THE ATMOSPHERE REQUIRED TO HOLD IN EQUILIBRIUM ISOLATED WATER DROPLETS OF VARIOUS SIZES

Diameter of Water Droplet μ	Percentage Supersaturation	
	at 0 C	at 21 C
100	0.002	0.002
50	0.005	0.004
20	0.012	0.011
10	0.024	0.021
5	0.048	0.043
2	0.120	0.107
1	0.240	0.214

the cloud. Because Table III shows that this degree of saturation is only very slightly above 100 per cent relative humidity for droplets larger than 10 micra in diameter, for such droplets it is possible to read "per cent of equilibrium saturation" instead of "per cent relative humidities" in Table II. Since most of the evaporation will occur at lower relative humidities, the time in which the atmosphere within a newly formed aerosol will reach a given percentage of equilibrium saturation will be *faster* than the time recorded under the corresponding percentage relative humidity in Table II.

Table II thus gives an upper limit to estimates of the time required for a newly formed water aerosol to achieve a specified degree of equilibrium with the atmosphere within it. In the same manner, mixing a preformed water aerosol with partially saturated air will cause rapid evaporation of droplets until equilibrium is again reached. In both cases, evaporation of the aerosol may be partial rather than complete; but if the aerosol has nonuniform size distribution, the smallest droplets may evaporate completely while larger droplets evaporate only partially.

The above situation is complicated by the presence of dissolved substances and electric charges in aerosol droplets.[6] These act to reduce the effective vapor pressure of the droplet surfaces and thereby reduce the degree of supersaturation required to hold the droplets in equilibrium.

Under the conditions of droplet contents of dissolved substances and electric charges encountered with nebulizers used for human therapy, the above interpretation of Table II is probably still valid.

Applying the above analysis to the practical problem of a nebulizer generating a water aerosol, Table II indicates that rapid equilibration of water vapor pressure within the newly formed aerosol must be expected. As soon as the aerosol stream emerges into the open atmosphere, mixing with unsaturated air will occur and the water droplets will evaporate either partially or completely. In order to avoid significant mixing with room air, all aerosol sampling should therefore be done as close as possible to the point where the aerosol stream leaves the nebulizer.

The temperature changes generated in the process of nebulization can cause further, less obvious, changes in droplet size. The air used for generation of a water aerosol becomes saturated in its passage through the nebulizer and in this process its temperature drops to the dew point, whose value depends on the initial temperature and degree of saturation of the air. Thereafter the air, which now constitutes the atmosphere within the aerosol, warms up again to room temperature and in the process tends to become unsaturated, requiring evaporation of water droplets to maintain equilibrium. This consideration appears to rule out methods for size analysis of water aerosols that permit a significant time interval to elapse between production and sampling of the aerosol.

ACCEPTANCE OF DROPLETS ON SAMPLING SURFACES

The present study indicates that there is a critical size for acceptance of aerosol droplets impinging against a sampling surface held in a vertical plane. Droplets of this critical size and smaller ones seldom register, while larger droplets do so with higher probability. A simple dimensional analysis indicates that the variables which determine this critical droplet size include the nature of the sampling surface, the nature of the aerosol and the linear velocity of the aerosol stream, while the probability of acceptance of a droplet varies as a higher power of its diameter.

In actual experiments, it is difficult to determine what proportion of the droplets impinging on a slide actually register on it. If a stream of a uniformly sized aerosol leaves no or only very few imprints when directed against a sampling surface, the droplet size must be below the critical size for acceptance under those particular experimental conditions. If, however, a nonuniformly sized aerosol is used, it is not possible to conclude solely from the evidence of a positive sampling slide, whether or not only the larger droplets in the aerosol are being accepted on the slide with a high probability.

The above reasoning suggests that standardization of a sampling procedure with a uniformly sized aerosol is a valuable safeguard against the

possibility of artifacts. In addition, comparison of the times required to saturate different sampling surfaces exposed to the same aerosol can give warning of a low probability of droplet acceptance on those surfaces that require substantially longer sampling times.

EXPERIMENTAL PROCEDURE

Of the six methods for size analysis described below, the "methylene blue" method contains significant modification of established practice, while the present adaptation of Roller's[10] "Stokes' law method" to liquid aerosols is novel. Aerosol samples were taken 1 inch from the outlet of nebulizers that are further described in a succeeding paper.[8] Droplet size or imprint size was measured with a Leitz microscope using a 15 x eyepiece micrometer.

Magnesium Oxide Method.—The classical method[5] is based on the fact that aerosol droplets will leave pits proportional to their size if they strike a magnesium oxide film with sufficient force to penetrate it. For use in droplet sampling, microscope slides were passed to and fro in the tip of the flame from a burning magnesium ribbon. In order to insure a fairly uniform deposit 100-200 micra in thickness, this procedure was repeated five times with 2-inch strips of ⅛-inch wide magnesium ribbon. Measurement of 100 of the *largest* discrete magnesium oxide particles on a sparsely covered slide gave a mean value of 1.66 micra, while the largest particle was 2.43 micra.

Using dibutyl phthalate aerosols,[8] imprints as small as 5 micra could be seen on some sampling slides, while on others hardly any imprints under 25 micra were visible. This variation is ascribed to "crust" formation of the surface of the films. As a result of this work, it was concluded that the magnesium oxide method is unreliable for sampling droplets that leave imprints under 30 micra in diameter.

Methylene Blue Method.—The method[5] as modified in this laboratory consists of impinging water droplets on a microscope slide covered with an even deposit of amorphous methylene blue. The water droplets dissolve the dye at the point of impact and push it to the periphery of a circle, leaving the dye concentrated as a dark band around a white circle. Thus, a permanent record of droplet size is obtained.

Methylene blue (Difco) was recrystallized three times by addition of an equal volume of acetone to a 1 per cent solution of the dye in water. The crystals were dried on a Buchner funnel, washed with acetone and dissolved in water to give a 2 per cent solution. This was filtered twice by gravity through a Whatman No. 42 filter paper. Microscope slides were scrupulously cleaned and placed for one minute in the filtered dye solution contained within a Coplon jar (approximately 3½ x 1¼ x 1¼ inches) in an oven at about 70 C, with the dye solution within ½ inch

of the top of the slide. Then it was removed with a pair of forceps and the top surface firmly stroked once up and once down with a Pyrex rod, taking care to make contact with all parts of the slide. The methylene blue solution dried rapidly in room air and was removed from the under surface of the slide with wet paper. The slide was then examined for suitability under the microscope. Slides at least partially covered with a homogeneous, amorphous, light blue deposit of methylene blue were retained as suitable for droplet sampling.

Film Method.—Farlow[1,2] has described a simple procedure by which photographic film can be coated with polyvinyl alcohol (PVA). The resulting film will retain imprints of water droplets that hit it. The only change in procedure of preparing the film was use of Kodak Clear Safety Leader Film No. 4 as base, since manufacture of No. 3 has been discontinued. Droplet imprints were measured under the microscope without prior development with phenylhydrazine vapor. The coated film turned progressively darker after several weeks of storage in a drawer, but there was no evidence of any change in the size of imprints. In the present experiments, the film method proved superior to the methylene blue method as regards ease of preparing the water-sensitive surface.

Lens Method.—The lens method of aerosol droplet sampling[5] consists of impacting droplets on a scrupulously clean slide. Because volatile drops rapidly evaporate, the method can only be used for nonvolatile liquids. Droplets spread on the slide to form a plano-convex lens, and the diameter of the equivalent spherical droplet can be calculated from three parameters: the diameter of the liquid lens, the focal length of the liquid lens, and the refractive index of the liquid.[5]

Sinclair[11] states that this method has sometimes been found unreliable: observation of droplets 4 micra in diameter, sized by the gravity fall method and also by weighing a known number of droplets, gave results 25 per cent too low by the lens method.[11] In the present authors' experience, the method proved to be satisfactory within its limits. Its disadvantages are that focal length measurements of small droplets are tedious. In addition, failure to clean the sampling slides by the same procedure causes serious variation in the correction factor required to convert lens diameter to equivalent drop diameter. Nevertheless, this method is probably the simplest available for absolute size determination of nonvolatile droplets that are nonuniform in size-distribution.

Oil Film Method.—In this classical method, water droplets are "fixed" by allowing them to impinge on a viscous liquid in which they are insoluble. Various types and mixtures of oils or jellies have been used for this purpose.[5,11] In the present investigation, water droplets were sampled on mineral oil, castor oil, Wesson oil and Mazola oil. Use of

coverslips coated with the sampling oil or jelly did not appear to increase the stability of sampled water droplets. Best results were obtained by spreading a thin film of "Lubriseal" (Arthur H. Thomas Company) on a microscope slide and placing the slide vertically in an oven at 40 C for ten minutes. The resulting slide was used for sampling droplets either directly on removal from the oven, or after cooling.

At the relatively high room temperatures of 25-29 C in our laboratory, solution of water droplets in the sampling fluid took place within time periods of seconds to hours, depending on the sampling fluid and on droplet size. Since solution is a surface phenomenon and since droplet surface is proportional to the square of droplet diameter, the time a water droplet of given size requires to dissolve in the sampling fluid can be expected to be proportional to the square of its diameter. In agreement with this hypothesis, smaller droplets dissolved very much faster than larger droplets.

The oil film method of aerosol sampling using active impingement rather than gravity settling was found to be poor on two counts. First, a long exposure time was required to collect any significant number of droplets on a slide, suggesting that most of the water droplets did not penetrate into the collection fluid. Secondly, the rate of solution of water droplets of apparent diameter 6 micra and under was quite rapid. On this account, the method was discarded as unsuitable.

Stokes' Law Method—The method as developed in this laboratory consists of placing the outlet of a nebulizer directly within the inlet at the bottom of a vertical separating chamber, and measuring the concentration of the effluent aerosol by means of a spectrophotometer. It is an adaptation of Roller's method[10] to liquid aerosols. Because of the long time-interval between production of the aerosol and the spectrophotometric measurement of optical density, the method only applies to non-volatile aerosol liquids.

As has previously been described,[9,10] size separation is effected in the central, large diameter portion of the settling chamber, where the linear air-flow velocity is a minimum. Depending on this minimum velocity, droplets smaller than a certain critical diameter are carried up through the settling chamber, while larger droplets fall back under their own weight. Results obtained with solid, irregular-shaped particles[9] showed that the size separation obtained with the Roller separator is in approximate agreement with Stokes' law. Since Stokes' law was derived for spheres, better agreement with Stokes' law might be expected for droplets, which come close to an ideally spherical shape. The separating chambers used were the series of 1⅛, 2¼, 4½ and 9-inch I.D. chamber* developed by Roller for his particle-size analyzer.[10] In addition, an 18-inch I.D. chamber described in a previous paper[9] and a 36-inch I.D.

*American Instrument Co., Inc., Silver Spring, Maryland.

chamber constructed specially for the present study were used. The exit tubing of nebulizers described in the next paper[8] were bent vertical, and secured within the inlet tube of all separating chambers by a suitably bored rubber stopper. Aerosols emerging from the top of the separating chamber were led to a spectrophotometer by a 1-inch I.D. rubber tube 2 feet in length. For the small droplet sizes investigated, the aerosols were relatively stable, otherwise a hole could have been bored through the bottom cover of the spectrophotometer to permit direct access of the aerosol to the spectrophotometer cell compartment.

The spectrophotometer was an a.c. model Fisher Electrophotometer. Only minimal modifications were required to convert it to an aerosol spectrophotometer. The cuvette carriage was removed, a plain glass microscope slide was taped over the photoelectric cell to protect it, and two 1¼-inch diameter holes were bored in front and on top of the hinged cover to the cell compartment, to serve as aerosol inlet and outlet. The light path across the aerosol was 4.7 cm. At the flow rates used (7 to 25 liters per minute), the cell compartment was filled to an equilibrium level within twenty seconds after the aerosol stream was turned on. Unfiltered white light was used in all determinations, and the instrument was set to give maximum response.

To use this aerosol spectrophotometer, the instrument was set at zero optical density with fresh air in the cell compartment. Then the aerosol stream was run in and after allowing twenty seconds for equilibration, the optical density of the aerosol was read. Now the aerosol stream was directed elsewhere (into a hood), the compartment cover raised to blow out the compartment, the cover closed again and the return to zero optical density checked. This sequence was repeated. The entire procedure was rapid and simple, and readings in the order of 0.5 optical density were reproducible to 0.5 per cent.

In an actual experiment, the volume air flow rate of pure air through the empty nebulizer and separating chamber was determined. Since at any given operating pressure the volume air flow rate through the nebulizer remained constant, this flow rate remained constant independent of the separating chamber used. Next the internal surface of the separating chamber was wetted with the liquid to be nebulized. Then the nebulizer was inserted and run for a time period at least three times that calculated as required to fill the chamber completely with aerosol. After this equilibration period, the relative optical density of the effluent aerosol was determined as described above. The same procedure was repeated with each of the six separating chambers.

The linear air flow velocity in the large diameter portion of the separating chamber was easily calculated from the measured volume flow rate and the internal diameter of the separating chamber. The diameter of the largest droplet leaving a separating chamber at this given air flow velocity was read off the Stokes' law curve for spherical droplets of

unit density, constructed from the data in Table IV.[7,9] Then this diameter (d_u) was converted to the diameter (d) corresponding to the actual density (ρ) of the aerosol liquid by the equation:

$$d = \frac{d_u}{\sqrt{\rho}}$$

In this manner, a value of optical density of the effluent aerosol and a corresponding value of the maximum droplet diameter in that aerosol

TABLE IV. EVALUATION OF STOKES' EQUATION (WITH CUNNINGHAM'S CORRECTION APPLIED) FOR THE TERMINAL VELOCITY OF SPHERICAL DROPLETS OF UNIT DENSITY, FALLING UNDER GRAVITY IN AIR AT 21C AND 760 mm PRESSURE

Droplet Diameter μ	Terminal Velocity of Free Fall Cm/Min
100	1788
50	447
20	71.9
10	18.11
5	4.61
2	0.771
1	0.208
0.5	0.0591
0.2	0.01331
0.1	0.00514
0.05	0.00224
0.02	0.000828
0.01	0.000403

was obtained for each of the six separating chambers used. From this data a size-distribution curve was plotted. The main assumptions in this method are that no change in droplet size occurs in the passage of the aerosol through the separating chamber, that no "channeling" occurs, and that Stokes' law is obeyed.

RESULTS

The experiments described below were greatly facilitated by appropriate use of close-to-uniformly sized aerosols.[8]

Film Method.—In Farlow's calibration method,[1] a water *suspension* of close-to-uniformly-sized *particles* is aerosolized. When the resulting nonuniformly-sized *droplets* are sampled on sensitized film, they leave imprints of varying size containing particles that can be counted. The diameter of a spherical water droplet that should contain the same number of particles as that counted within a given imprint is easily calculated from the concentration of particles in the original water suspension. Then the ratio of the diameter of the imprint to the diameter of the corresponding spherical droplet gives the required calibration factor.

Farlow[1,2] used latex spheres of 0.514 ± 0.011 micra diameter and corn smut spores of 7.8 ± 0.3 micra diameter for his calibration. In

the present experiments, red blood cells and corn smut spores were used. Normal red blood cells have a mean diameter of 7.2 micra and a mean corpuscular volume of 87 cubic micra.[12] When 200 corn smut spores* were measured under the microscope, a mean diameter of 6.8 micra and a size-range of 6.1-7.9 micra for two-thirds of the spores was determined. Since these spores are roughly spherical, their average volume is taken to be 165 cubic micra.

Two different types of calibration experiments were done. The first differed from that used by Farlow only in that a table was drawn up for the particular particle concentration used for aerosol production, giving the diameters of spherical droplets containing from 1 to 120 particles. This table permitted direct conversion of the particle count for each imprint to an equivalent spherical diameter. The sample of normal blood used contained 5.5 billion red cells per cubic cm; two cell counts made three days apart using a clinical hematocrit chamber agreed within 1 per cent.‡ The hematocrit was 48.5 per cent and the hemoglobin concentration 16.0 g/100 ml blood. This blood was diluted 1 to 50 with isotonic saline and aerosolized with continual agitation in a commercial nebulizer operated unmodified at 0.4 atmosphere pressure, in order to produce relatively large and nonuniform droplets.[8] Four coated film cuttings (each about 3.0 x 3.5 cm) were exposed to the aerosol stream for about ½ second at 1 inch from the outlet of the nebulizer. On each of these cuttings, diameters of 100 droplet imprints were measured and the number of red cells contained in each imprint was counted. By use of the table described above, a conversion factor was calculated separately for each imprint. The average conversion factor for four samples of each 100 droplets was 0.67, 0.57, 0.56 and 0.55, giving a mean factor of 0.59.

The second type of calibration experiment involved use of close-to-uniformly sized aerosols obtained from a modified Vaponefrin nebulizer[8] at an operating pressure of 0.4 atmospheres, using a twenty-second sampling period. Aerosols were prepared from various dilutions of blood in isotonic saline, and the total number of drops and the total number of red cells were counted on thirty to fifty fields of the microscope, so that approximately 500 drops and a corresponding number of red cells were counted on each of four film cuttings. The results obtained at different blood dilutions are shown in Table V, and are in good agreement with each other. The diameter of droplet imprints in the last column of Table V was obtained by direct measurement of fifty randomly sampled droplets on each of the four film cuttings used for each blood dilution. The variations in this measured diameter are probably unrelated to the degree of dilution of the blood. The ratio of the mean diameters recorded in

*Stem Laboratories, Inc., Oklahoma City 11, Oklahoma.

‡Thanks are due Mrs. Bobbie Wallace for making these counts.

the last two columns of Table V give a conversion factor of 0.87. An identical experiment with corn smut spores at a concentration of 46.85 million/ml gave an average equivalent spherical droplet size of 22.5 micra, which is in good agreement with the above value of 22.2 micra. The measured mean diameter of droplet imprints was 28.8 micra, giving a conversion factor of 0.78.

These data show that the above method gives well reproducible results for the mean equivalent spherical droplet diameter, while the measured imprint diameters show a larger random variation. There appears to be poor agreement between the mean conversion ratio of 0.82 obtained above with droplets of average imprint diameter 27.5 micra, and the factor of 0.59 obtained by the first type of experiment using larger, nonuniformly sized droplets with mean imprint diameters of approximately 100 micra. In this connection it is relevant that the data of Farlow and French[2] show a large increase in the conversion ratio with decrease in droplet size. Thus, for imprint diameters of 20, 15, 10, 5 and 2 micra, the smoothed data of Farlow and Franch[2] give conversion ratios of 0.57, 0.60, 0.65, 0.73 and 1.28. One possible explanation for this apparent change in calibration factor with change in droplet size is that it is an artifact caused by water clinging to and evaporating from the marker particles of droplets that have impinged on the sensitized surface. If this explanation is correct, the artifact should be especially serious at small droplet sizes and at small ratios of droplet diameter to particle diameter, and these conditions actually correspond to those under which the experimentally determined calibration factor increases. It will therefore be assumed that in the absence of marker particles the calibration curve of imprint diameter against spherical droplet diameter would be a straight line through the origin. For this reason, the calibration factor of 0.59 determined at the larger droplet size will be accepted. This factor is in good agreement with that of approximately 0.56 obtained by Farlow and French for droplet imprints in the 30-180 micra range.

The calibration experiments with red cells were done using isotonic saline suspensions, while those with corn smut spores used water suspensions. The slightly lower conversion ratio obtained with corn smut spores may be related to the tendency to obtain smaller imprint sizes with saline, which is described below.

Effect of Salt Concentration on Imprint Size.—Air at 0.4 atmosphere pressure was used to nebulize water or isotonic saline with a Vaponefrin nebulizer with S-shaped outlet[8] and the resulting droplets were sampled on sensitized film. With water, the mean imprint diameter of a total of 400 droplets measured on eight film cuttings was 30.8 micra, while with isotonic saline 200 droplets measured on four film cuttings averaged 27.5 micra. The difference between these results was statistically significant ($P < 0.01$).

TABLE V. CALIBRATION OF FILM SAMPLING METHOD WITH AEROSOLS OF ISOTONIC SALINE CONTAINING A KNOWN CONCENTRATION OF RED BLOOD CELLS

Blood Dilution	Red Cell Conc. Million/Ml	Volume Containing 1 Red Cell Ml	Number Droplet Imprints	Number Red Cells	Ratio Cells to Drops	Volume Average Drop Containing Ratio Cells to Drops Ml	Volume Average Drop Corrected for Red Cell Content Ml	Mean Diameter of Equivalent Spherical Droplet μ	Measured Mean Diameter of Imprint μ
Infinite	0	—	—	—	—	—	—	—	27.5
1▶100	55	18.18×10^{-9}	1926	658	0.342	6.22×10^{-9}	6.18×10^{-9}	22.8	24.9
1▶ 50	110	9.09×10^{-9}	2847	1756	0.636	5.76×10^{-9}	5.70×10^{-9}	22.2	25.3
1▶25.6	215	4.66×10^{-9}	2123	2660	1.25	5.83×10^{-9}	5.72×10^{-9}	22.2	24.3
1▶14.8	372	3.07×10^{-9}	1254	2314	1.84	5.65×10^{-9}	5.49×10^{-9}	21.9	27.1
	Mean	—	—	—	—	—	5.75×10^{-9}	22.2	25.8

TABLE VI. COMPARISON OF DROPLET SIZING BY THE FILM, THE METHYLENE BLUE (M.B.) AND THE LENS METHODS

Nebulizer Operation	Measured Imprint Sizes			Corrected Sizes and Ratios			
	Film (Water) μ	M.B. (Water) μ	Lens (Mazola Oil) μ	Film x0.59 μ	Film (Corr.) / M.B. (Uncorr.)	Lens x0.45 μ	Film (Corr.) / Lens (Corr.)
Vaponefrin B, S-shaped outlet—2.4 A.P.	16.6	23.2	24.8	9.8	0.422	11.2	0.87
Pen-i-sol, 3-coil outlet—0.7 A.P.	24.1	33.5	30.0	14.2	0.424	13.5	1.05
Vaponefrin B, S-shaped outlet—0.4 A.P.	31.0	42.9	38.7	18.3	0.427	17.4	1.05
Mean	—	—	—	—	0.424	—	0.99

A similar experiment was done using the methylene blue method to sample droplets. Using water and 0.9, 3.0 and 6.0 per cent saline solutions, mean imprint diameters for 200 droplets sampled at each concentration were, respectively, 24.5, 24.5, 21.1 and 21.3 micra. Comparing the combined data for water and 0.9 per cent saline with the data for 3.0 and 6.0 per cent saline, a significant ($P < 0.01$) reduction of imprint size with higher salt concentration was obtained.

Lens Method.—Working with dibutyl phthalate (Fisher Scientific Company) of refractive index 1.55, a correction factor of 0.35 that varied from 0.30 to 0.38 in six sets of experiments was evaluated by May's method.[5] The variability of the correction factor seemed to correlate with changes in the cleaning procedure used on the sampling slides. For Mazola oil (a commercial cooking oil containing mainly glycerol trioleate) a refractive index of 1.52 and a correction factor of 0.45 was determined, with the latter varying from 0.43 to 0.46 in three sets of experiments. When these correction factors were applied to the measured diameter of droplet lenses, the diameter of the equivalent spherical droplet was obtained.[5]

Comparison of Film, Methylene Blue and Lens Methods.—Table VI compares the droplet sizes of water and Mazola oil nebulized under the same conditions in different nebulizers that produce close-to-uniformly sized droplets.[8] Each figure reported is the mean of 200 imprint diameters except for the film method, where two operators independently prepared water-sensitive film, exposed it to the water aerosols and measured 200 drops for each aerosol size. The results obtained by the two operators agreed to better than 2.1 per cent for each aerosol size.

The ratio of droplet sizes as determined by the film and by the methylene blue (M.B.) methods is constant within about 0.1 per cent for the data in Table VI. Thus, if the conversion ratio of 0.59 for the film method is correct, the conversion ratio for the methylene blue method is 0.424.

While the agreement between the calculated spherical size as obtained by the film or by the lens method is satisfactory, this agreement does not confirm the validity of either method, since the results were obtained with different liquids, namely, water and Mazola oil. If it is assumed that these two methods both give valid spherical droplet sizes, then the conclusion can be made that the spherical droplet size of water or Mazola oil aerosols produced under these identical conditions is quite similar.

Standardization of the Magnesium Oxide Method.—Because this method was unreliable below imprint sizes of about 30 micra, only the largest droplets produced by a nebulizer giving a nonuniform size-dis-

tribution could be used. Because of the large variation in the size of these droplets, the calibration results are only an approximation.

Water was nebulized in the Mist-O_2-Gen nebulizer at an air pressure of 2.4 atmospheres.[8] The droplets were impacted on magnesium oxide and on methylene blue sampling slides. The data obtained by measuring 450 imprints by each sampling method gave a conversion ratio of 1.01 for sampling water aerosols on magnesium oxide-covered slides.

Stokes' Law Method.—Figure 1 shows some cumulative size analysis curves obtained with the Stokes' law method when Mazola oil was nebulized. The 50 per cent points of these curves gave figures for the average spherical diameters of the droplets in these aerosols. Such values were generally between one-third and one-half of the corrected mean values of 12 to 18 micra that were obtained by direct impaction of these droplets on clear slides and subsequent size determination by the lens method.

In the Stokes' law method, several factors may act in concert to produce a low value for the mean spherical droplet diameter of the aerosol stream. The first factor is a differential loss of larger droplets at the entrance to the separating chamber and on the walls of the chamber. The second factor is the phenomenon of "channeling," which is particularly serious in the thirty-six-inch and in the eighteen-inch diameter separating chambers. The third and perhaps the most important factor is the relatively high surface area of the smaller droplets, which gives them a disproportionately larger light absorption on the basis of equal weight. Conversely, microscopic methods of size determinations may stress unduly the largest droplet sizes.

These considerations indicate that the Stokes' law method of droplet sizing is not strictly comparable with microscopic measurements of droplet imprints.

COMMENT

The theory and experiments described indicate that there are many pitfalls in determining the size-distribution of liquid aerosols, especially if the liquid is volatile, such as water. The aerosol evaporates rapidly on mixing with unsaturated air and must, therefore, be sampled close to the outlet of the nebulizer. Because the air within a nebulizing chamber cools as it becomes saturated in the process of aerosol formation, it subsequently warms up to room temperature and causes partial evaporation of droplets to maintain the rising equilibrium saturation pressure.

All of the droplet sampling methods investigated require that the droplets have sufficient momentum for acceptance on the slide surface. In general, this means that large and fast-moving droplets will be impacted while small and slow-moving droplets may not leave an imprint on the slide. Calibration experiments were done mainly with close-

to-uniformly sized droplets[8] for which possible errors due to this cause are minimal, because the chance of acceptance is similar for all droplets in the aerosol.

The film method developed by Farlow and French[1,2] appears to be

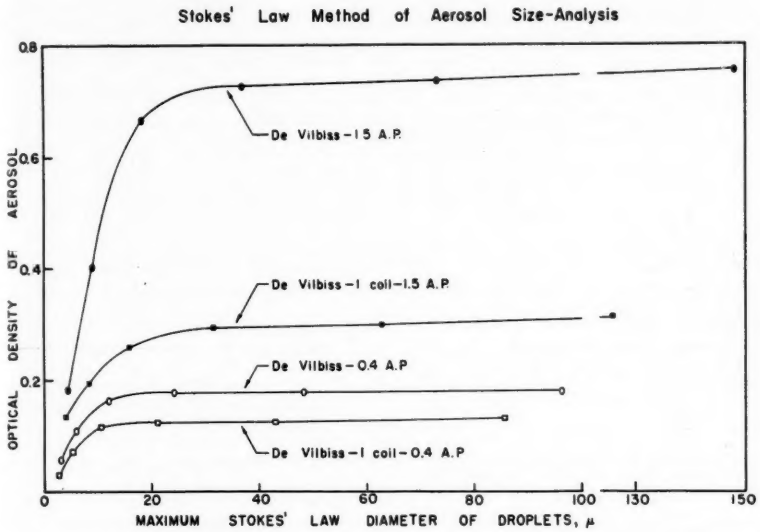

Fig. 1. Stokes' law method of aerosol size-analysis. The aerosol liquid is Mazola oil.

superior to the methylene blue method as regards ease of preparing the water-sensitive surface. Future improvement of the Stokes' law method for sizing nonvolatile liquid aerosols should certainly be possible. This might take the form of running variable fractions of the output of a nebulizer into a single (rather than multiple) separating chamber, passing the effluent through the spectrophotometer in a closed system and subsequently determining the volume air flow rate of this effluent.

SUMMARY

The rate of evaporation of water droplets, as calculated from classical equations, is sufficiently swift that water aerosols should be sampled close to the nebulizer outlet. Various methods for sampling water aerosols are compared, and of these the film method developed by Farlow and French and to a lesser extent the methylene blue method are satisfactory. For these methods, the factors required to convert the measured imprint diameter to the diameter of the equivalent spherical droplet are, respectively, 0.59 and 0.42. A Stokes' law method for determining the size-distribution of nonvolatile liquid aerosols is described, which is

based on the use of Roller separating chambers, combined with optical density measurements in a spectrophotometer.

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TRUTH AND FALSITY

"A proposition is either true or false, but our knowledge is for the most part so limited as to make it impossible to be rationally certain of either its truth or falsity. To form a rational belief, we must have some pertinent knowledge. Occasionally, such knowledge may be sufficient to justify our certainty that Socrates was not an American citizen; and we are equally certain that Hitler should have remained a house painter. On the other hand, between the extremes of certainty there is a rainbow of shadings of belief corresponding to the degree of our knowledge.

"In a sense, it is undoubtedly true that our rational beliefs are subjective. Still, if we are convinced of the objective truth or falsity of all propositions, we cannot, if we wish to be rational, permit ourselves to be guided by mere intensity of belief. As a matter of principle, faulty conclusions based on limited knowledge and correct reasoning are infinitely preferable to correct results obtained by faulty reasoning. It is only thus that we faintly approach the life of reason."—EDWARD KASNER and JAMES NEWMAN, *Mathematics and the Imagination,* Simon and Schuster, New York, 1940.

IMMUNIZATION AFTER INTRADERMAL AND SUBCUTANEOUS INJECTION OF ASIAN INFLUENZA VACCINE

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THE PRESENT STUDY was done in order to clarify the usefulness of intradermal vaccination as compared to subcutaneous immunization for Asian influenza. The vaccine used was monovalent type A Far Eastern strain (Jap 305-57) of influenza vaccine in a concentration of 200 CCA units per cubic centimeter. The pertinent question to be answered was, *"Is intradermal vaccination immunizing?"*

The introduction of new vaccine characteristically is accompanied by conflicting information concerning adequately immunizing potencies and techniques. Published reports and recommendations in the literature concerning Asian influenza vaccine have reflected this confusion. Evaluations of the adequacy of 0.10 cc of vaccine administered intradermally have been particularly conflicting. In most of these studies, either the complement fixation (CF) test or the hemagglutination inhibition (HI) test has been used as an indicator of immunity. Studies emanating from the National Institutes of Health and the U.S. Public Health Service have used both tests, however, as providing the best estimate of immunity.[1,4]

Both tests have also been used in the present study to assess antibody rise following vaccination with monovalent Type A Asian influenza vaccine.

PROCEDURE

Volunteers were requested among the employees of the Brooklyn Regional Office of the Veterans Administration: 366 persons of both sexes, aged twenty to seventy, responded.* These were divided by chance into two unequal groups. The larger group was selected for intradermal vaccination with 0.10 cc of material, since it was felt that adequate data existed in other studies dealing with antibody titers following subcutaneous immunization. The smaller group was inoculated subcutaneously in the standard manner with 1.0 cc of vaccine.

For the purpose of evaluating effectiveness of the immunizing procedure, 10 cc of blood was withdrawn from each subject just prior to vaccination and again, two weeks later. Both sets of samples were frozen and then titrated against the same antisera after all blood collection was

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*With the kind co-operation of Dr. Philip T. Casesa, Director of Clinic, Veterans Administration Outpatient Clinic, Brooklyn, New York.

completed. A viral antigen using the Japanese 305-57 strain of influenza Type A was used in the CF test, and a virus isolate which was typed against an anti-Jap-305-57 hyperimmune chick serum, for the HI test.†

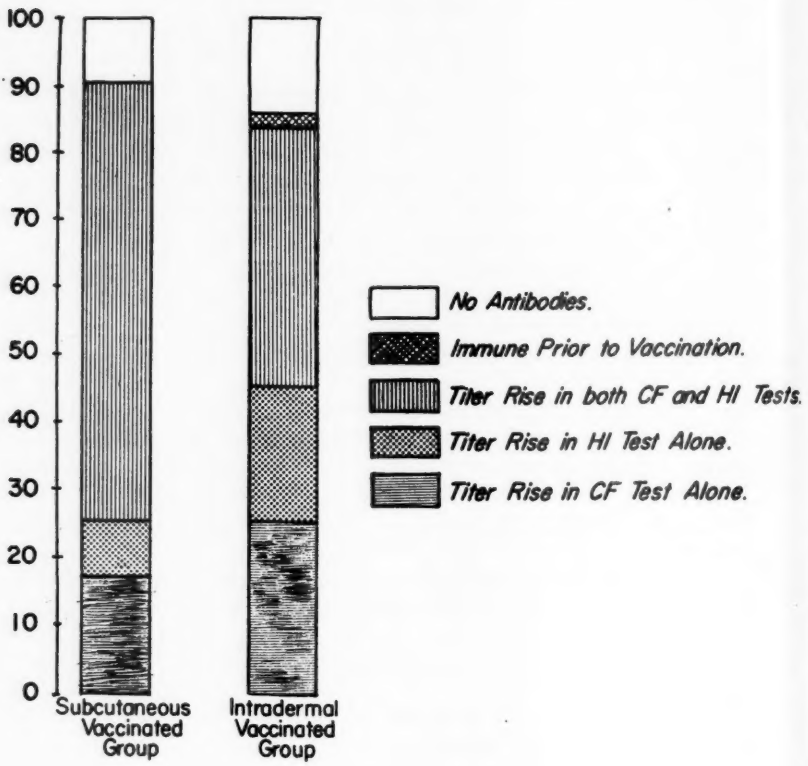

Fig. 1. How immunity was achieved in the two groups.

RESULTS

From the original group of 366 persons, complete data could be obtained for only 276. Of these, 204 had been vaccinated intradermally and seventy-two, subcutaneously. Five subjects in the intradermally injected group were found to have initial antibody titer levels indicating immunity. The intradermal injection, therefore, provided a "booster" effect for them. In the remaining 199 intradermally vaccinated subjects only eighty-four (41 per cent) showed a 1:4 rise or greater in both CF

†All laboratory studies were made by the Virology Laboratories of the Board of Health of New York City, through the courtesy of Dr. Daniel Widelock, Assistant Director of Laboratories, whose invaluable assistance is gratefully acknowledged.

and HI titers, while ninety-one (45 per cent) demonstrated a rise in one of the two tests. If only one test of immunity had been used, evidence of antibody rise would have been missed in a considerable number of subjects. Only twenty-four persons intradermally vaccinated failed to indicate a rise in antibodies following intradermal vaccination (Table I and Fig. 1).

TABLE I. COMPARATIVE RISE IN ANTIBODY TITER, 1:4 OR GREATER, TWO WEEKS AFTER VACCINATION.

Vaccination Method	Number of Subjects	Number Responding				Total Rise	Already Immune	No Increase in Titer
		CF Only	HI Only	Either CF or HI	Both CF and HI			
Subcutaneous	72	13	6	19	47	66	0	6
Per cent		17	8	25	67	92	0	8
Intradermal	204	51	40	91	84	175	5	24
Per cent		25	20	45	41	86	2	12

These results were quite comparable with those achieved in the subcutaneously inoculated group. Of seventy-two persons so vaccinated, forty-seven (66 per cent) responded with a rise in titer measured by both tests, and nineteen (25 per cent) responded to only one of the two tests. Six subjects (8 per cent) failed to show any rise in antibody

TABLE II. PERCENTAGE OF INCREASE IN ANTIBODIES AS REVEALED BY EITHER OR BOTH SEROLOGIC METHODS

Method of Vaccination	Total Showing Increase	No Increase	Immune Prior to Vaccination
Subcutaneous	86	12	2
Intradermal	92	8	0

titer. Serum dilutions for all of these tests were 1:4 or better; thus these findings would indicate that significant protection was achieved two weeks after inoculation in 86 per cent of the intradermally vaccinated group and in 92 per cent of the subcutaneously vaccinated group (Table II). Although the United States Public Health Service now recommends that 400 rather than 200 CCA units per cc be used for optimal protection,[3] it is noteworthy that the antibody levels measured in this study were quite comparable with those recorded in other published studies using more concentrated vaccines injected subcutaneously.[1,2]

At the level of 1:32 or greater, the HI titer rose in approximately 45 per cent of subcutaneously injected individuals, and in 31 per cent of intradermally inoculated persons (Fig. 2). In patients recovering from actual attacks of Asian influenza, 75 per cent show titers of 1:32 or better.[11]

DISCUSSION

The value of intradermal injection, both for purposes of immunization and for increasing levels of titer (i.e., "booster") has been known and previously described.[6] In administering Schick tests to asthmatic subjects, Dr. M. M. Peshkin has determined that even doses of 1 unit given intradermally produce an increase in blood titer. A similar use of the Moloney Test in which 0.10 cc of 1:100 diphtheria toxoid is administered intradermally has also been followed by an increase in blood titers for diphtheria antibodies.[6]

Some years ago, studies of polyvalent influenza vaccine showed significant immunizing effects achieved with the use of intradermal vaccine.[10] Nevertheless, although the intradermal route is generally recognized to be safer than is intramuscular or subcutaneous injection, disagreement is still widespread concerning the adequacy of immunity achieved.

When the vaccine for Asian influenza was still newly developed, the problem was further complicated by the variety of opinions and recommendations concerning standardization, potency, and techniques at the time of initial release. Conflicting data in the literature did not help to resolve this confusion.

The Armed Forces, for example, had employed concentrations of from 400 to 800 CCA units per cc during their vaccination campaigns in the spring and summer of 1957.[1,4] Nevertheless, by the time the vaccine was generally released in the autumn of 1957, the available potency was only 200 CCA u/cc. A study released at about that time indicated that vaccine from one manufacturer containing 506 CCA u/cc, was not much better in stimulating antibody production than vaccine from another containing 200 CCA u/cc.[1] Nevertheless, manufacturers at first recommended that 1 cc of the 200 CCA u/cc vaccine be administered subcutaneously or intramuscularly, with a "booster" injection of .50 cc in from two to seven days. Children could be given .50 cc subcutaneously, or, .10 cc intradermally.[3] The duration of immunity was then estimated as ranging from four to fourteen months; booster doses were to be given either four to six or twelve months after initial immunization.[2] In November, the Public Health Service recommended that a single dose of 1 cc of the 400 CCA-type vaccine be injected subcutaneously, and that those who had received vaccine containing 200 CCA u, whether intradermally or subcutaneously, be given a second subcutaneous injection of this potency.

Several limited studies were reported, usually based on small numbers of subjects and on only one laboratory measurement of antibody production. Thus, Boger and Liu[2] reported on the basis of HI tests that only eight of twenty-two elderly patients showed a rise in antibody titer four weeks after intradermal injection, whereas twenty of twenty-two patients given 500 CCA units subcutaneously so responded. On the other hand, Sigel et al,[9] using two lots of vaccine containing 100 and 200 CCA units,

reported good results in adults injected intradermally, particularly when booster injections were given five weeks after initial vaccination. These authors also reported in their communication that the results in children injected intradermally were superior to those attained with subcutaneous

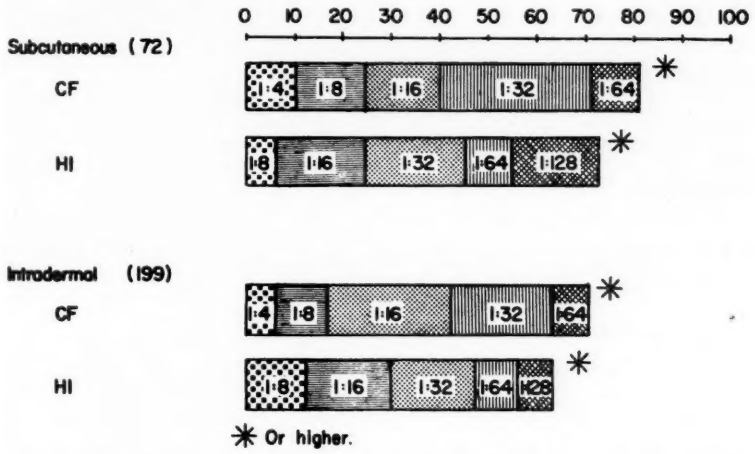

Fig. 2. Serologic response to subcutaneously and intradermally administered vaccine.

vaccination. Both HI and CF tests were done in this study. Although not reporting results, Love[5] in another communication implies satisfactory response obtained with use of 0.15 cc to 0.20 cc of vaccine containing 200 CCA u/cc injected intradermally. Sadusk,[7] on the other hand, questions the efficacy of intradermal immunization, implying that only actual challenge with influenza virus, rather than rise in antibody titer, can confirm successful immunization. This point was elucidated, however, by Bell et al of the United States Public Health Service,[1] who found that subcutaneously administered vaccine conferred "moderate but incomplete protection against Asian influenza" which was subsequently artificially induced.

Another factor complicating evaluation of results using various methods of vaccination is the relatively low level of antibody titer often observed in vaccinated subjects. During the epidemic of Asian influenza, comparatively low titers were also recorded following recovery from actual infection.[8] Jensen attributes this phenomenon to "the nature of antibody response when a new antigen is encountered."[4]

The results reported in this paper, therefore, suggest that the observed rises in antibody titer were sufficient to afford considerable protection if we consider a rise in titer at any level to be immunologically significant.

The gains in titer were comparable when measured by both the CF and HI tests. Finally, they were well within the range reported by other observers using this new material.

SUMMARY AND CONCLUSIONS

1. Intradermal injection of 0.10 cc of Asian influenza vaccine, containing 200 CCA u/cc produces a rise in antibody titer comparable to that achieved with subcutaneous injection of 1.0 cc of the same vaccine, when measured by both CF and HI techniques.

2. The technique can be used to immunize subjects known to be sensitive to egg.

3. In times of short supply, the intradermal technique permits available stocks of vaccine to be increased ten-fold.

4. Intradermal inoculation should be given more widespread trial, and should be considered the technique of choice especially during times of short supply.

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"The art of diagnosis demands in addition to skill and wisdom a lavish expenditure of time, sympathy and understanding. The good doctor knows his patients through and through. His knowledge is bought dearly, but he finds his reward in that personal bond which forms the greatest satisfaction in the practice of medicine."—DONALD HUNTER, M.D., The Art of Diagnosis, *Central African J. Med.*. 1:5 (Sept.) 1955.

REACTIONS TO INFLUENZA VACCINE

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REACTIONS to influenza vaccine have been under study within the United States military departments ever since the first field trials in 1943. Since that time, more than 15 million doses of this material have been given to Army personnel alone. Because immunization of military personnel is carried out primarily to maintain the maximum number of troops fit for duty, the significance of reactions is most usefully estimated by measuring the degree to which they cause non-effectiveness. This paper will present selected data to assess the importance of reactions to influenza vaccine considered from this point of view.

VACCINE MANUFACTURE*

First, however, it should prove useful to review the composition of the antigen. The nature and extent of reactions may be more clearly appreciated against this background.

The various methods by which influenza vaccine is manufactured will be briefly outlined, with special reference to those steps in the process whereby antigenic materials are added.

A volume of 0.1 to 0.2 ml of seed virus, diluted 10^{-3} to 10^{-6} in saline, is inoculated into the allantoic sac of eleven-day-old embryonated hen's eggs. The eggs are incubated at 33-38° C for thirty to forty-eight hours, candled, and the dead embryos discarded. Unless the vaccine is to be prepared by red cell adsorption and elution, the eggs are chilled, usually overnight at 2-5° C. The allantoic fluids are then harvested.

The viral content of these fluids may be concentrated by centrifugation, protamine precipitation, or red cell adsorption and elution. The first of these employs a high speed centrifuge which operates at about 50,000 RPM to collect the virus particles. The virus-containing sediment is suspended in 0.1 M phosphate buffer to a volume about 2-10 per cent that of the original allantoic fluid. This buffer may contain 0.025 per cent (1:4,000) formalin. In some processes this suspension is then further clarified by slow-speed centrifugation.

When protamine precipitation is the method employed, formalin-inactivated allantoic fluids are dialyzed and protamine is added. (The protamine meets the specifications of that used for protamine-insulin.) The virus-protamine complex is sedimented by slow-speed centrifugation and then suspended in buffered saline containing 1:10,000 thimerosal.

With the exception of one process whereby virus is inactivated by

*The courtesy of the manufacturers in providing this information freely and completely is to be commended, and is gratefully acknowledged.

ultraviolet irradiation, formalin and thimerosal are added for inactivation and stabilization. Ethylene oxide, 0.5 per cent, is sometimes added to the viral concentrate for further inactivation; it is later removed by exposure to reduced pressure. The final formalin concentration is stated to vary from 1:2,000 to 1:10,000. In each case the thimerosal concentration is 1:10,000.

The red cell adsorption and elution method of manufacture differs sufficiently as to require separate description. With this method, the viable eggs are harvested without chilling. During this procedure, the major blood vessels are ruptured so the fluids will contain many red cells. Adsorption of the virus occurs in the cold for eighteen to twenty-four hours. The supernatant egg fluids are discarded and replaced with 1/10 volume of saline. The virus is eluted from the cells at 37° C, after which most of the red cells are removed by centrifugation. Inactivation is accomplished by the addition of formalin at a final concentration of 1:4,000 at 2-10° C. The final vaccine is preserved with thimerosal at a concentration of 1:10,000.

VACCINE COMPOSITION

It can be seen from the review of the manufacturing process that there are several components of influenza virus vaccine other than influenza virus and saline. The absence of other constituents which one might expect to be present may also be noted; some of these warrant specific comment.

In these days an individual without some experience with antibiotic agents is a rarity, and one immediately asks about the presence of these. At the present time, no manufacturer uses any antibiotic agents in the manufacturing process. Similarly, none are routinely used in the seed inoculum. Up to 100 micrograms of streptomycin per egg may be added occasionally to the seed inoculum prior to injection into the eggs. This is said to be impossible to detect by sensitive assay methods even in the harvested crude fluid prior to concentration. No company reported the use of penicillin at any stage of manufacture. The presence of silk antigen in certain biologic products from the use of silk filters in their preparation has been noted as a cause of severe allergic reactions.[1] However, this material is not used by any manufacturer in the production of influenza vaccine.

Efforts were made to estimate the composition of the protein content of the vaccines. For example, the manufacturers were asked to estimate what percentage of the finished vaccine represented original allantoic fluid. A range of percentages from less than 1 to as high as 6 per cent was estimated to be representative. (It must be remembered that these percentages represent concentrations of allantoic fluid, not egg albumen or yolk.)

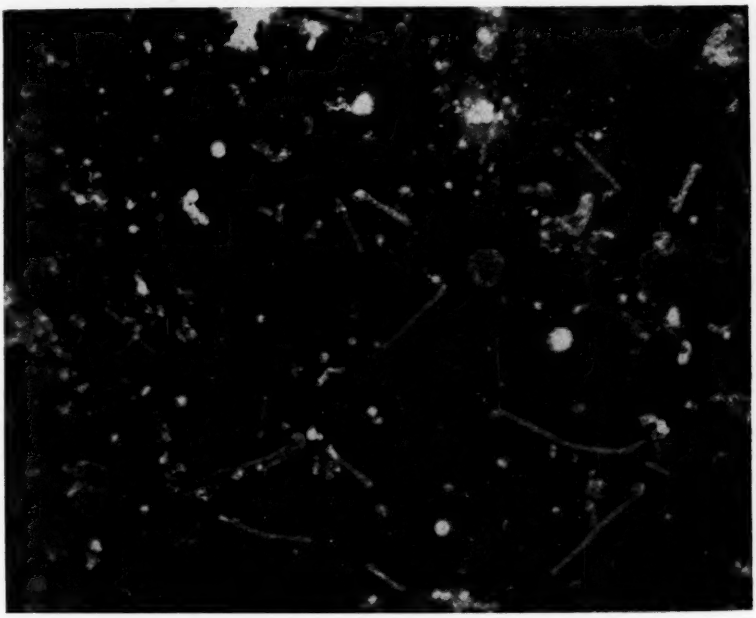

Fig. 1. Electron micrograph of partially purified Asian influenza vaccine (x15,000): Virus preparation and micrograph by R. E. and R. S. Hartman, Walter Reed Army Institute of Research, Washington, D. C.

Using another approach, the total nitrogen was found to be in the range of 0.015-0.08 mg N/ml of centrifuged vaccine. The values for protamine-precipitated, and red cell adsorbed and eluted products are somewhat higher, in the range of 0.10-0.16 mg N/ml, since the concentrating method here adds protein which is present in the final vaccine. Using a figure of 36,000 CCA (chick cell-agglutinating) units/mgN for highly purified influenza virus, the nitrogen derived from virus in a 400 CCA unit vaccine might approximate 0.011 mg N/ml from virus alone. Thus, under certain circumstances of manufacture, as must as 80 to 90 per cent of nitrogen in the vaccine could be derived from virus, although the value may be as low as 10 per cent. When the virus strain has been recently isolated, as the Asian strain was, as little as 1 per cent of the protein in early vaccines may have been virus.

An electron micrograph taken by Hartman and Hartman at Walter Reed Army Institute of Research may be used to help visualize the ratio of virus to other material in the vaccine. It was prepared for another purpose, but, with certain reservations, it is applicable here.

The material used was an early lot of commercial vaccine, egg grown and concentrated by red cell adsorption and elution. It was further puri-

fied by two cycle differential centrifugation which eliminated more than 99 per cent of the non-viral matter. After this purification, the material was re-suspended in saline, placed on the grid and shadowed with uranium. The resultant picture is seen in Figure 1.

Several distinct types of particles may be identified. Most prominent are the rod-shaped structures, whose long axis is ten to fifteen times as long as the transverse diameter. The Hartmans cautiously state that these are "presumably viral in nature." They are antigenic, hemagglutinating and probably infective. With only mild reservations, it is fair to state that they represent influenza virus. However, it should be noted that they are characteristic of recently isolated and unadapted virus. More characteristic of the appearance of older, well-adapted strains are the round structures of the same diameter as the rods. In addition to the virus, one can see quite a bit of semi-amorphous material. Some of this is egg protein; some is probably red cell detritus; some may be soluble antigen. What is significant, however, is its amount. Even after 99 per cent reduction of the extraneous material, it still approximately equals viral material in volume. Thus, one would expect that non-viral material, even if less antigenic than the virus component, could be responsible for as many reactions because of its quantity. It is for this reason that, although the routine influenza vaccination programs in the armed services have been on a mandatory basis, personnel administering the vaccine are always instructed to ask regarding known egg or chicken protein sensitivity, so that probable reactors may be exempted from vaccination.

MILITARY EXPERIENCE

Long[2] has reported the nature and frequency of reactions observed during the 1943 field trials and the 8 million dose program of 1945. In the former period, systemic reactions followed administration of the vaccine in about 20 per cent of those vaccinated. The reactions were characterized by generalized aching, chilliness, malaise and mild fever. Only a small proportion of those experiencing reactions of this type required hospitalization. There were no anaphylactoid reactions encountered in the groups studied at the time, although there were reports of two instances of cutaneous eruption following vaccination. In 1945 there was considerable variation in the occurrence of reactions. Reports from different organizations indicated that as few as seven and as many as 85 per cent of vaccinated personnel experienced generalized reactions of varying degrees of severity. The most common percentages reported ranged from 25 to 50 per cent. The symptoms described were similar to those reported previously. The onset was usually within eight to ten hours after vaccination. Few required hospital care. Local reactions, consisting of burning and stinging of the arm with some residual soreness and stiffness, were not uncommon. In addition to the local and generalized reactions, there were reported three reactions of an anaphylactoid nature, two of

TABLE I. REACTIONS* TO INFLUENZA VACCINE
U. S. Army 1953-55

Year	Number of Inoculations	Reactions							
		Total		Mild		Moderate		Severe	
		Number	Rate†	Number	Rate†	Number	Rate†	Number	Rate†
1953	1,088,316	12,872	11.83	12,680	11.65	183	0.17	9	0.01
1954	1,289,709	5,743	4.45	5,375	4.17	293	0.23	75	0.06
1955	1,058,795	3,001	2.83	2,905	2.74	81	0.08	15	0.01
Total	3,436,820	21,616	6.29	20,960	6.10	557	0.16	99	0.03

*Reported in Outpatient Report, DD Form 444 (Feb. 1, 1951).
†Rates expressed as reactions/1,000 inoculations.

which were fatal. All were considered to have been allergic responses to the egg component of the vaccine in individuals previously sensitized to egg protein.

Seal's[3] (1954-55) report of experience in Navy and Marine training bases is similar. Although a high percentage of vaccine recipients had transient, mild, local or systemic symptoms, less than 0.05 per cent (0.5 per 1,000) required admission to an infirmary or hospital.

MATERIALS, METHODS AND RESULTS

Attempts to measure the absolute magnitude of reactions to influenza vaccine outside the structure of a well-controlled study are unrewarding. Moreover, such observations are not comparable to those from other experiences unless they are similarly controlled, but meaningful information may be generated using a relative measurement. Values so developed must be interpreted carefully because of the many variables which affect the determination as to whether or not a given event is counted as a "reaction." But comparison of these data with similar values for other antigens collected under the same circumstances and presumably responsive to the same variables can provide a basis for a reliable estimate of their relative magnitude and impact for military use.

This sort of analysis has been carried out for the years 1953-55, using "days lost" as the unit of measure. At that time the Outpatient Report (DD Form 444) noted the number of inoculations of each vaccine administered in Army medical facilities and the number and severity of reactions.* Reactions were defined as "mild" if they were tolerated by a patient on a duty status; "moderate" reactions were those which caused entry to the excused-from-duty status for not more than forty-eight hours. "Severe" reactions, then, exceeded these limits, *i.e.*, to from more than two days lost up to and including fatal reactions.

The reactions reported for each year and for the period as a whole, are summarized in Table I. The 21,616 reported reactions constitute 0.6 per cent of the almost 3½ million doses administered. Ninety-seven per cent

*Most of the vaccine recipients were active-duty Army personnel, some were other military personnel, and some were military dependents.

of these subjects (20,960) were treated while on duty. The more significant figure is the 656 (557 plus 99) who were admitted to excused-from-duty status and charged against the diagnosis of "reaction to influenza vaccine." This number is 0.2 per 1,000 inoculations, roughly com-

TABLE II. RATES* OF REACTION TO INFLUENZA AND OTHER VACCINES 1953-1955

Vaccine	Reactions			
	Total	Mild	Moderate	Severe
Influenza	6.29	6.10	0.16	0.03
Typhoid (B)	6.86	6.37	0.47	0.02
Smallpox (P)	39.30	38.20	0.90	0.21
Smallpox (R)	24.43	22.29	2.04	0.10
Tetanus (B)	7.18	6.92	0.24	0.03

*Rates expressed as reactions/1,000 inoculations. Data compiled from Outpatient Report, DD Form 444 (Feb. 1, 1951).
(B)=Booster.
(P)=Primary.
(R)=Revaccination.

parable to the 0.5 per 1,000 which Seal reported. Although variation is observed from year to year, particularly in the proportion treated while on duty status, the rates for the "moderate" and "severe" reactions are generally of the same order of magnitude.

More meaningful insight into the significance of these data may be gained by comparing them with the data which refer to reactions to other commonly used immunizing agents. This comparison is made in Table II. Each vaccine listed is one routinely administered, and, in this case, given as a single immunization, *i.e.*, not as a part of a series. Thus, the typhoid and tetanus data refer to booster doses only (B), and smallpox vaccine is separated into primary vaccinations and re-vaccinations (P and R). In each category, with the exception of severe reactions to typhoid boosters, reactions to influenza vaccine were reported at rates equal to or lower than those to other antigens. When measured by this parameter, the impact of reactions to influenza vaccine is of a magnitude which is considered acceptable for other antigens.

Reactions reported from the Fall 1957 vaccine program of the Army have been collated separately. The material administered was 1.0 ml of 200 CCA unit A Asian virus vaccine, given subcutaneously. The Outpatient Report has been changed so it no longer contains the data described above. However, the "Clinical Record Cover Sheet" (prepared on each patient discharged from "excused-from-duty" status) provides similar information. This form contains the diagnosis, manifestations of illness, and the number of days "lost," either in hospital or quarters. All reports indicating that admission was because of a reaction to influenza vaccine were analyzed for these attributes.

In Table III is tabulated the frequency distribution by number of days lost. The 277 admissions reported were almost evenly divided between hospital and quarters. As the mean length of stay is only slightly greater for hospital rather than for quarters cases, one may surmise that selection

TABLE III. ADMISSIONS TO HOSPITAL OR QUARTERS FOLLOWING INFLUENZA VACCINATION IN 1957

Days Lost Per Admission	Admissions*		
	Hospital	Quarters	Total
1	33	69	102
2	53	26	79
3	36	31	67
4	16	7	23
5	0	2	2
6	2	1	3
7	0	0	0
8	0	1	1
Total	140	137	277
Mean	2.31	1.94	2.12

*Reported on Clinical Record Cover Sheet.

for admission to hospital as opposed to quarters may have been as much a matter of availability of facilities as of severity of illness. The illnesses were of short duration; 90 per cent of the admissions were for less than four days. In accordance with the previous criteria, 181 were "moderate" reactions, and ninety-six "severe." As there were approximately one million inoculations given, the gross "lost-time" reaction rate reported was thus near 0.3 per 1,000, which is quite similar to previous reports.

TABLE IV. REACTIONS TO INFLUENZA VACCINE IN 1957
Manifestations Reported* in 181 Cases

Symptom	Frequency	Symptom	Frequency
Fever	161	Respiratory symptoms	52
Malaise	107	Back or chest pain	16
Chills	101	Edema or urticaria	10
Headache	79	Gastrointestinal symptoms	8
Myalgia	51	Faintness	5

*Reported on Clinical Record Cover Sheet.

The primary manifestations of illness were tabulated in an effort to categorize more definitively the excused-from-duty status classified by the attending physician as reactions to influenza vaccine. One would expect that a recognizable pattern would emerge which might be characteristic of that condition. On the other hand, one might find symptom combinations typical of some other condition, or at least of such a nature as to cast doubt on the validity of the diagnosis.

The data of Table IV show that both of these expectations are valid. One-hundred-eighty-one of the records included information about the

manifestations of illness. Most of them were associated with fever. Generalized constitutional symptoms of malaise and chills accompanied more than half the cases. Headache and myalgia were less frequent. However, some combination of these manifestations may readily be accepted as characteristic of systemic reaction to influenza vaccine as seen in the past. It is not surprising to find it this year.

Listed on the right side of the table are other manifestations either less frequent or less characteristically associated with vaccination reactions. The fifty-two instances of respiratory symptoms are made up of twenty-six cases of "cough," fourteen of pharyngitis or sore throat, eleven of coryza and one of bronchitis. Since many vaccination programs were carried out while common respiratory disease was occurring, it is reasonable to believe that the occurrence of most of these symptoms following the vaccination was co-incidental. The validity of pain of the chest and back as manifestations of reactions is not evident. Probably true reactions are the three cases of generalized edema and the seven of urticaria—all of which promptly responded to conventional therapy. The eight cases of nausea, vomiting and diarrhea are likely coincidental.

A careful study of all reports of admissions said to be associated with reactions to influenza vaccine failed to reveal any instance of the more serious manifestations. Myelitis or other neuropathy, such as reported by Warren[4] from the 1953 program, or anything resembling significant anaphylaxis was completely absent. Likewise, the type of immediate allergic reaction manifested by severe massive urticaria which Denny[5] described this year was not seen, at least to that degree.

It is apparent that the syndrome caused by constitutional reaction to influenza vaccination is not pathognomonic, and that almost any disorder which occurs shortly after such vaccination is likely to be classified as a reaction to the vaccination; the cited figures thus undoubtedly overestimate the number of reactions and the true magnitude of the problem.

SUMMARY AND CONCLUSION

A review of influenza vaccine manufacturing procedures indicates the antigenically polyvalent nature of this material. The proportion of the total protein which is viral in nature varies widely.

In military experience, systemic reactions of fever, chills, aching and malaise have been very common, but only two to five per 10,000 vaccine recipients required hospitalization. Serious reactions have been very rare. Influenza vaccine has led to less "time lost" from reactions than have other common immunizing agents. Reactions to influenza vaccine prepared from (Asian) virus were not significantly different in number, severity or nature from those previously observed.

The amount of time lost from duty because of reactions to influenza vaccine as now manufactured is insufficient to act as a bar to the general use of this product in the military population.

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TENACITY

"Among all the qualities that the experimentalist must possess there is no doubt that none has greater value to him than tenacity. He has planned a series of experiments intended to determine the worth of a hypothesis; he carries them out but instead of finding in the results of these practical tests a plain, clear, and precise answer, he obtains nothing but approximate if not incoherent results. He intended to solve a scientific problem by various methods in order to give his solution more stability and solidity, and now the methods employed lead to incongruous results or at least results that seem so. Will he let himself be discouraged, give up the game because difficulties have arisen? If so he should renounce the experimental career, for the path of the experimentalist is littered with obstacles that he must surmount by necessity if he wishes to progress and reach his goal. He only is fit to experiment who senses a rugged joy when he comes to grips with difficulties, who rushes headlong to solve them and will devote all his time, all his forces, all his energy and his entire soul to the task. He will first of all and to the end search for the cause of the experimental incoherences that have upset him so much, and he will almost always find that they are owing to lack of accuracy in some conditions of his experiments. With a little attention he will overcome this defect. He will examine his methods of research, will criticize them most rigorously, will scrutinize their qualities and shortcomings in order to eliminate those that have some flaw and that he had accepted too swiftly in the beginning. In most cases this will be enough to eliminate the obstacle yet not always, and it may well be that the difficulty in spite of his care remains unsurmounted, perhaps unsurmountable."—MAURICE ARTHUS, *Philosophy of Scientific Investigation*, Baltimore, The Johns Hopkins Press, 1943.

THE ELECTROENCEPHALOGRAM IN ALLERGIC CHILDREN

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MOST allergists agree that hypersensitivity reactions occur in the central nervous system. Despite the increased awareness and clarification of allergy as related to clinical disorders of the central nervous system, many facets of neuroallergy remain in the realm of speculation and controversy. It is only fair to assume that the electroencephalogram, which records the electrical potentials of the brain, might increase our understanding of allergic disorders of the central nervous system.

In 1948, Dees and Lowenbach[2] were the first to describe a specific focal abnormality in the electroencephalograms (hereafter referred to as EEGs) of allergic children. They observed occipital dysrhythmia in approximately one-half of eighty-five children with all types of allergic disease. Chobot and associates[1] reported that 32 per cent of eighty allergic children had abnormal EEGs, but they did not confirm the findings of Dees and Lowenbach, particularly those related to occipital dysrhythmia. In a series dealing with a relatively homogenous allergic group, Holmgren and Kraepelien[9] noted an incidence of 36 per cent abnormal EEGs in 100 asthmatic children. They concluded that there were no specific changes in the EEGs of the asthmatic children, although there was occipital dysrhythmia in twenty-two of the patients studied. In 1951, Dees and Lowenbach[2] reported that in thirty-seven allergic children with seizures, occipital dysrhythmia occurred in almost 75 per cent of the thirty-seven patients studied. Dees[3] suggested that occipital dysrhythmia be included as one of several diagnostic criteria for the diagnosis of allergic epilepsy.

We wish now to report our EEG findings in a group of allergic children. Over a two-year period of interpreting EEGs at a large children's hospital, one of us (B.B.), was impressed by the paucity of EEG abnormalities in allergic children. Further, when abnormalities were discerned, they appeared to be non-focal. Since these observations had not been recorded previously, it seemed worthwhile to gather evidence of our own.

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In our study, we planned to use refined techniques with particular emphasis on "sleep" EEGs. None of the authors previously mentioned had resorted to sleep activation. Publications by Gibbs[5] and Gibbs and Low[7] stress the importance, simplicity and practicability of sleep, particularly in the study of childhood epilepsy. They noted that the incidence of seizure discharges in the EEG was more than doubled when patients were asleep. Furthermore, sleep tracings give valuable information in patients with temporal lobe elipesy and "thalamic" disorders.

MATERIAL AND METHODS

We examined the waking EEGs of twenty-five allergic children (fourteen boys and eleven girls), all from the private practice of one of us (J.G.). Tracings were obtained during sleep in sixteen of the twenty-five. Only children with one or more major hypersensitivities such as asthma, atopic dermatitis (eczema), rhinitis or recurrent upper respiratory disorders were studied. The symptom-complex "migraine," was excluded because the role of allergy in migraine is not clear, and other factors may account for any EEG changes observed. Twenty-two of the patients had more than a single type of allergy. The allergic disorders had been present for from two to eleven years. Although the information regarding family history is not always completely accurate, it is of interest that close relatives of seventeen patients had a positive family history of allergy.

The ages of our patients ranged from five to twelve years. More than 50 per cent were between five and eight years of age. Technically satisfactory EEGs are difficult to secure in patients below the age of five. Thus, it was considered best to eliminate this age-group from the study. Also excluded were children with organic brain disease—epilepsy, and any other chronic disease states, including diabetes—which might be associated with significant changes in the EEG. We studied only patients whose allergies were not under control. In our clinic, a patient is classified as "controlled" when he has been symptom-free for a period of one year.

A patient is designated as allergic when evidence indicated that the clinical state was due to a specific allergic reaction and when that allergic stimulant provoked an exacerbation of the allergic symptoms. Laboratory aids to the diagnosis of allergy were nasal smears and complete skin testing. Scratch and intradermal testing were employed and all results were personally checked by one of us (J.G.). Each patient's allergic studies included a complete history, physical examination, and a radiological examination of the chest. Each patient was also subjected to neurologic appraisal and only those with normal findings were accepted for this study. When the EEGs were performed, allergic rhinitis was present in nine of the twenty-five patients, and two of the twenty-five had evidence of atopic dermatitis.

ELECTROENCEPHALOGRAM METHODS

Electroencephalogram examinations were made by means of an eight-channel Grass apparatus, using unipolar and bipolar placement of electrodes. Activating procedures of over-ventilation (three minutes) and natural sleep were carried out when possible. When the child did not sleep spontaneously, chloral hydrate and/or seconal were used in an attempt to induce sleep.

The pattern of the EEG is modifiable by such movement artifacts as opening and closing of the eyes. In children especially, restlessness and anxiety may cause transitory over-ventilation of the lungs, thus causing significant EEG changes. One of us (B.B.) was present at each recording to observe the degree of the patient's co-operativeness and to record movements, artifacts, the state of consciousness and other factors that might modify the record.

As far as possible, all EEGs were performed when the children had been without allergic medication for at least three days. Also, asthmatic patients were not studied during an acute asthmatic attack since the role of anoxia may alter the true picture of the EEG.

Each child had one EEG. The tracings were interpreted independently by B.B. who knew the clinical history of the child, and by G.E. who had no such historical information.

Criteria for normal waking EEGs.—

Ages five to seven: Five to eight per second activity with interspersed four to six per second frequencies. Voltage of 25 to 150 microvolts.

Ages seven to nine: Frequency of seven to ten with scattered five to seven per second waves. Voltage 25 to 150 microvolts.

Ages nine to twelve: Frequency of seven to fifteen with six to seven per second bursts. Voltage 25 to 100 microvolts.

Standard for Abnormal Waking EEG.—

1. Frequencies which are faster or slower than those defined as normal under our classification; either diffuse, focal or paroxysmal.

2. So-called seizure discharge: (a) Single or multiple spikes, (b) Spike followed by a slow wave component. (c) Slow waves as noted under number 1.

3. Focus—Localization of an abnormality to a well-defined area or when the abnormality is maximal in a well-defined area. Focus can be: (a) Slow wave, (b) Spike, (c) Spike-wave.

4. Asymmetry—Differences in homologous areas of both voltage and frequency.

5. Over-ventilation—Assumes diagnostic importance only when there are paroxysmal spike or spike-wave discharges evoked during the three-minute period of overbreathing.

Drowsiness and Sleep Electroencephalograms.—Just as the waking EEG varied considerably from age group to age group, similar changes also occured during slumber as we proceeded from one age group to another. Furthermore, the pattern obtained in drowsiness and sleep showed very remarkable alterations in cortical activity. In our study, patients were examined only during drowsiness and light sleep. They were aroused whenever the EEG went beyond the light sleep pattern.

Normal Drowsiness.—

1. Paroxysmal 2-5/sec high voltage slow waves.
2. Paroxysmal 5-8/sec high voltage slow waves particularly in frontals.
3. Low voltage in all leads with single and scattered 2-5/sec high voltage slow waves.
4. Low voltage fast to 20/sec in all leads.

Normal Light Sleep.—

1. Biparietal Humps—High Voltage Spike-like waves which generally are diphasic and last ⅓ of a second. These occur most often in the three to nine-year-old group. Concomitant high voltage disturbance noted in other leads.
2. Bursts of twenty to 30 per second fast frequencies are scattered between Biparietal humps.
3. Fourteen per second spindles are seen in the parietal area of patients in all ages of childhood.
4. Twelve per second spindling in the frontals occurring independently or bilaterally.
5. Sharp waves and slow spikes in occipital areas bilaterally.

Abnormal Sleep and Drowsiness.—

1. Any record which failed to conform to the pattern described above as normal was considered abnormal.
2. All seizure discharges, foci and assymetry were classified abnormal.

Electroencephalograms were classified as normal, mildly abnormal, or grossly abnormal waking and sleeping EEGs. Mildly abnormal EEGs included those with alterations in frequency. Those grossly abnormal showed seizure discharges, foci, asymmetry, and abnormal responses to overventilation.

The interpretation of each EEG incorporated a precise definition of the abnormal features, *i.e.*, "This EEG is grossly abnormal because of a spike focus lateralizing to the right temporal area."

RESULTS

Twenty-three of twenty-five patients studied had normal waking EEGs. All sixteen sleeping EEGs were within normal limits. Two EEGs were classified as mildly abnormal because of alterations in frequency, the

two records displaying scattered slowing without lateralizing abnormalities. Sleep tracings in these patients were normal. No evidence of occipital dysrhythmia or other focal discharges was noted in anyone of the twenty-five waking and sixteen sleeping EEGs. Normal waking and sleeping EEGs were present in the nine patients with allergic rhinitis. The two patients with atopic dermatitis had normal waking tracings. Sleeping EEGs were not obtained in these two patients.

DISCUSSION

The studies here reported differ significantly from those of Dees and Lowenbach[2,4] and of Dees[3] and of Holmgren and Kraeplien[9] in that occipital dysrhythmia was noted as a prominent finding in their series and was not noted in ours. We also did not observe the other types of abnormalities reported by Chobot.[1] Since the patients of Holmgren and Kraepelien were like our own and unlike those of Dees and Lowenbach and of Dees in that they were free from convulsive disorders, an adequate explanation is lacking to explain this discrepancy between our findings and those of the other authors. The possibility exists that this might be based on a difference in the interpretation of the EEGs. No criteria of what constitutes a normal EEG were given by Chobot, and the other authors merely give an illustrative tracing of a normal EEG as compared with an abnormal EEG in an allergic child. For this reason, and for purposes of future studies by others, we have included the details of what we term a normal EEG.

Our results should not be construed as disproving the concept of a susceptibility of the vascular network of the human brain to allergenic stimulation. Although the series is small, we believe the results are significant because of the extremely small number of abnormal tracings. These observations lend support to the concept that the EEG changes in the allergic child are minimal. Specifically, our series does not support the findings of focal or lateralizing abnormalities in the tracings of allergic children. The subject deserves further investigation of a larger series of patients with the use of refined techniques and rigid criteria of what is normal.

SUMMARY

1. Electroencephalographic study was made of twenty-five allergic children between age of five to twelve, who were subject to one or more major allergies.

2. Of twenty-five EEGs made when the child was awake, twenty-three were within normal limits.

3. Tracings made during sleep in sixteen of these patients were also within normal limits.

4. Tracings mildly abnormal because of slowing were encountered in two patients but no focal changes were noted.

5. The validity of previous reports which show a large proportion of allergic children with EEG abnormalities is questioned.

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DISCOURSE ON METHOD

"Good sense is, of all things among men, the most equally distributed; for everyone thinks himself so abundantly provided with it, that those even who are the most difficult to satisfy in everything else, do not usually desire a larger measure of this quality than they already possess. And in this it is not likely that all are mistaken; the conviction is rather to be held as testifying that the power of judging aright and of distinguishing truth from error, which is properly what is called good sense or reason, is by nature equal in all men; and that the diversity of our opinions, consequently, does not arise from some being endowed with a larger share of reason than others, but solely from this, that we conduct our thoughts along different ways, and do not fix our attention on the same objects. For to be possessed of a vigorous mind is not enough; the prime requisite is rightly to apply it. The greatest minds, as they are capable of the highest excellences, are open likewise to the greatest aberrations; and those who travel very slowly may yet make far greater progress, provided they keep always to the straight road than those who, while they run, forsake it."—RENE DESCARTES. *Discourse On Method,* Everyman Edition.

DISTRIBUTION AND IMMUNOCHEMICAL PROPERTIES OF HUMAN TISSUE AND TUMOR ANTIGENS II.

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IN Part I of this series,[3] some of the technical difficulties that are encountered in the study of human tissue antigens were outlined. I also described therein the methods we employed and their advantages, and presented some preliminary data to illustrate the difficulties of proving that a given tissue contains a specific antigen.

In the present paper, I will limit myself to a few examples of the problems that are common in this kind of study, and towards the end of this paper, some theoretical aspects of auto-immunity and how it may relate to tumor immunity will be discussed.

Example 1.—Two rabbits were immunized with a human carcinoma of the ovary. The resulting antisera (anti-Ca overy 4a[3] and anti-Ca ovary 4b) were absorbed with lyophilized pooled plasma and then tested against the homologous carcinoma of the ovary as well as other tissues, using the gel diffusion technic of Ouchterlony as described previously.[3] Anti-Ca ovary 4a produced at least three lines with the homologous antigen preparation, and occasionally one or two lines with the extracts from other carcinomas. Anti-Ca ovary 4b was more specific and produced three lines only with the homologous extract. The obvious interpretation would be that the two sera reacted with different antigens, some of which were present in the homologous extract as well as in other tumors, whereas the other antigens were more specific in that they were lacking from the heterologous tissues we examined. In order to check this obvious explanation, we set up the following experiment:

In one plate (Fig. 1) we placed the two antisera in cups B and D, the homologous antigen was in A and the heterologous extract from a carcinoma of the breast, was in cup C. In another plate (Fig. 2) we placed the antisera in reservoirs A and C, and homologous and heterologous extracts in reservoirs D and B respectively. The relative specificity of anti-Ca ovary 4b was apparent from both plates; however, the finding that the two antisera reacted with the same antigens in the homologous extract (Fig. 2) was unexpected. That they did react with

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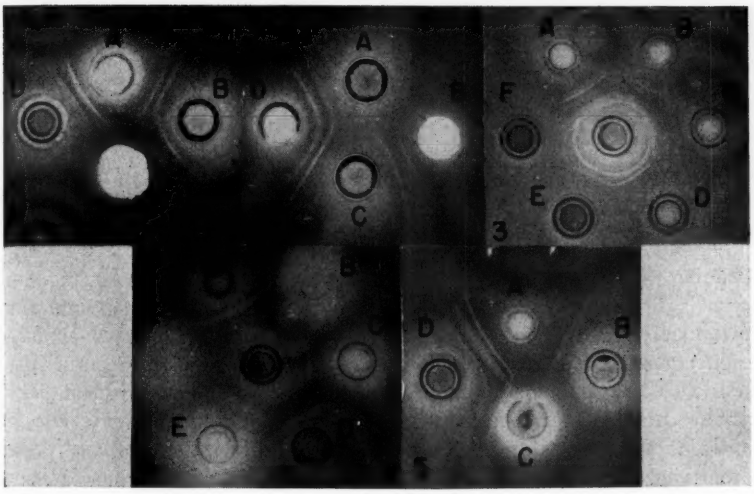

Fig. 1. (A) Ca Ovary 4—40 mg/ml, (B) Anti-Ca Ovary 4a, (C) Ca Breast —40 mg/ml and (D) Anti-Ca Ovary 4b.

Fig. 2. (A) Anti-Ca Ovary 4b, (B) Ca Breast—40 mg/ml, (C) Anti-Ca Ovary 4a and (D) Ca Ovary 4—40 mg/ml.

Fig. 3. (*Center*) Anti-Chronic Myelogenous Leukocyte Serum, (A) Homologous Antigens—20 mg/ml, (B) Homologous Antigens—10 mg/ml, (C) Homologous Antigens—5 mg/ml, (D) Homolgous Antigens—2.5 mg/ml, (E) Homologous Antigens—1.0 mg/ml and (F) Homologous Antigens—0.5 mk/ml.

Fig. 4. Anti-Acute Leukemia Leukocyte Serum. (A) Homologous Leukocytes—20 mg/ml, (B) H.Ep.#2—30 mg/ml, (C) Lymphnode—40 mg/ml, (D) Homologous Leukocytes—10 mg/ml, (E) Normal Spleen—20 mg/ml and (F) Normal Liver—20 mg/ml.

Fig. 5. (A) Chronic Myelogenous Leukocytes, (B) Anti-Chronic Myelogenous Leukocyte Serum Absorbed with Sediment of Chronic Lymphocytic Cells, (C) Chronic Lymphocytic Leukocytes and (D) Anti-Chronic Myelogenous Leukocyte Serum.

the same antigens was apparent from the coalescence of the lines; the theory of the double gel diffusion technique and its repeated experimental confirmation with well defined antigen-antibody systems leaves us no other alternative. The fact that both antisera react with the same antigens of the homologous tumor extract whereas only one of them reacts with antigens in the heterologous extract suggests several possibilities:

1. The quantitative properties of the two antisera are different. For example, one antiserum might produce a line with relatively little of a given antigen, whereas the other would require large amounts of that antigen. In order to check this possibility, both antisera were tested against decreasing amounts of the homologous extract. It was found that both antisera reacted to the same endpoint, and consequently possibility 1 must be rejected.

2. The two antisera react with the same antigenic molecules of the

homologous extract, but against different antigenic determinants on these molecules. Some of these determinants are present on the molecules of both the homologous and heterologous extracts, but a few are relatively specific for the homologous antigens. This explanation has been used for other well defined systems like multiple myeloma proteins[5] and gamma-1 macroglobulins.[6] Whether it is applicable to the present system remains to be seen.

Example 2.—In a previous paper[3] we have emphasized the need for defining the term "absent." It has recently been suggested that malignant cells lack certain antigens present in normal cells without giving any information as to the quantity of antigen used or the minimal amount of homologous antigen still detectable by the antiserum. The meaninglessness of such claims is apparent from the following experiment done as part of an extensive study in collaboration with Dr. Miller on leukocyte antigens.[7] Using a potent antiserum against cells from a patient suffering from chronic myelogenous leukemia, we titrated a homologous antigen preparation. Starting with cup A, twofold dilutions were pipetted into each adjacent reservoir. The pertinent feature of this experiment is that the big antigenic molecules closest to the antigen cups are no longer detectable after a fourfold dilution, and that a subsequent twofold dilution does not even deflect the line produced by the antigen of the next higher concentration. This deflection of a line by even trace amounts of antigen has often been observed with other antigen-antibody systems. From our own experience, we now know that it occurs primarily with those antigens whose diffusion coefficient is greater than that of antibody; antigens whose diffusion coefficient is smaller and which consequently diffuse more slowly, produce lines that curve away from the antibody reservoir[3] and these lines are not readily deflected by even considerable amounts of homologous antigen in the adjacent reservoir (Fig. 3).

Let us now return to the consequences of this experiment. The concentration of 5 mg/ml of homologous leukocyte preparation still produces an easily detectable line that curves away from the antibody reservoir. We have tested preparations from other forms of leukemia, prepared in an identical manner, which do not produce this line at even higher concentrations. However, at very high concentrations, it became apparent that the antigen was present in these heterologous leukocytes.

But now we must consider another complication. Leukocytes from leukemic patients are never homogeneous and usually include a few granulocytes. Since our antiserum was made against granulocytic cells, it would not be surprising that, as we raised the concentration of the heterologous cells, antigens contributed by the few contaminating granulocytes would be detected. We are fortunate in having at our disposal two strains of human leukocytes obtained from the buffy coat of the blood of patients with acute monocytic leukemia. These cells are now

grown in tissue culture and they contain some of the antigens found in granulocytic cells; other granulocyte antigens, however, cannot be detected in these cells, even when their extracts are used at 100 times the minimal concentration at which the homologous antigens still react. It should be emphasized that the availability of such pure strains of human leukocytes, as well as of other human cells grown in tissue culture, is going to assume increasing importance in the immunological studies of tissue and tumor antigens, but it should be remembered that these cells are grown under abnormal conditions and may consequently have lost some of their original antigenic properties.

Example 3.—Finally, I would like to show you another example of the difficulties one may have in deciding on the antigenic specificity of a cell. The antiserum[7] was against white cells from a case of acute leukemia with promyelocytes (65 per cent) and myelocytes (34 per cent). Some of the antigens detectable by this antiserum are not very specific, because they also occurred in some carcinoma cells grown in tissue culuture (H.Ep.#2). But, as you can see, this antiserum produced one strong line, close to the antigen reservoir, with the homologous leukocyte extract. This line was still detectable at 10 mg/ml but not at 5 mg/ml (Fig. 4). When this leukocyte extract was compared with tissue extracts, no corresponding line was seen with H.Ep.#2, a lymphnode extract, spleen, or liver. The greatest differential is a factor of 4. Given these data, would *you* call this antigen specific for the leukocytes in relation to the tissues it was compared with?

Before leaving the subject of the leukocyte as a source of cellular antigens attention should be directed to one of the shortcomings of the technique we have been using: it can detect only those antigens that are soluble under the conditions of the test. However, it is easily possible to determine whether the insoluble residue of the cells contains a given antigen that is not detectable in the saline soluble fraction. For example, using an anti-chronic myelogenous leukemic serum,[7] we failed to produce one of the lines with an extract of cells obtained from a patient with chronic lymphocytic leukemia. The antiserum was subsequently absorbed with increasing amounts of the insoluble residue of the heterologous cells and retested. From Figure 5 it is apparent that this absorption removed antibody against those components the two cell extracts had in common; however, the homologous extract still reacted with the absorbed serum. In contrast, it was found that absorption with similar amounts of homologous insoluble sediment removed all antibody.

A discussion of the prospects of cancer immunity invariably results in the following remark: "There cannot be any immunity because the body cannot become immunized against itself." This begs, of course, two questions:

1. *Does the body really not produce antibody (immunity) against itself?*

2. *Is the tumor still antigenically (and genetically) like the host?*

You all know about Ehrlich's conviction that immunity, and antibody, was produced only against material foreign to the animal, because he felt that if the animal were to produce auto-antibodies it would result in its own destruction. This dogma of the "horror autotoxicus" has dominated immunological thinking for several decades, and only recently have some of its staunchest defenders begun to abondon it. (Of course, we know that the "body" seems to care very little whether its products are harmful or not; every day you see patients whose immune systems produce substances which cause discomfort and even death). However, let us examine the facts:

Auto-antibodies have been observed against: eye lens proteins, casein, thyroglobulin, brain substance, testicular matter, erythrocytes[1,8] and some of these antibodies are known to lead to auto-allergic conditions, which are, of course, of interest to this audience.

The defenders of the idea that antibody is produced only against foreign substances have pointed out that the antigens giving rise to auto-antibodies are really exceptional—they are either "outside" the body (eye lens), or isolated from the circulation (thyroglobulin, casein) or they develop late in embryological life (brain matter, testicular substances), before the "self markers" are formed. (But then, γ-globulin is formed even later). During the last few deades, however, auto-immunization has been implicated in a whole host of diseases,[8] and in these instances the antigen is undeniably part of the "self." How then are such auto-antibodies formed? Many hypotheses have been developed, most of which have recently been criticized in a thoughtful paper by Grabar.[2]

I think that many of the above difficulties can be eliminated by rephrasing the "horror autotoxicus" hypothesis so that it will take into account all known and well-established facts; for example, "No detectable antibody (immunity) is formed against those antigens that are present in sufficiently large concentration in the animals' antibody (immunity) forming cells." This hypothesis has certain advantages: it substitutes "antibody forming cells" for "itself," and the term "detectable antibody" does not eliminate the possibility that antibody is indeed formed but immediately fixed by excess antigen. It is apparent that the exceptional antigens listed above are localized in certain cells, and it may therefore be assumed that they are absent from antibody forming cells like the plasma cell. Moreover, the hypothesis indicates that under certain conditions auto-immunity may be developed against any other antigen that is organ or cell specific. Consequently, if it can be shown that a given

tumor contains an antigen that is absent from the cells responsible for antibody production, we may ultimately hope to obtain an auto-immune reaction against it.

The second question which was raised above, i.e., whether the tumor is antigenically identical with the host's cells, can as yet not be answered because our knowledge of the antigenic composition of normal and malignant cells is still rudimentary.

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LOGIC AND THE LAW

"And I find it difficult to conceive of a better education in Logic than that which is given to the Student who reads Law as a pupil with a barrister in large practice. It is an education which consists in consulting Legal Textbooks, looking up cases in Law Reports and following the procedures in the Law Courts.

"And the signal advantage which attaches to a Legal (as distinguished from a Medical, or Architectural, or Engineering) Education is this: that we are dealing here not (as we are in Medicine and most other professional training) with the judgments of isolated reasoners, but with judgments many of which have been subjected to revision in a whole series of Higher Courts.

"The reader will appreciate that in our Legal System every point of Law is brought up first before a Magistrate; then, if that does not settle the point, before a County Court Judge; then before a regular Court of First Instance; then, if there still remains any doubt about it, before the Court of Appeal; and finally, if the issue is of sufficient importance, before the Highest Appellate Court—that of the House of Lords.

"There is, as I have already pointed out, very little trace of such logical subordination in Medicine; for here the judgment of the General Practitioner or Specialist is practically never submitted to higher authority."—SIR ALMROTH WRIGHT, *Alethetropic Logic*, Wm. Heinemann, London, 1953.

THE EFFECT OF DRUGS IN ACETYLCHOLINE-INDUCED BRONCHIAL OBSTRUCTION

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THE INDUCED asthmatic attack is a useful means of studying the pathophysiology of asthma and also of evaluating the effect of bronchodilator drugs on depressed ventilatory function. Pollens, allergens, and known bronchial obstructing drugs such as histamine[1,3,11,17,20,25,26] and acetylcholine[10,18,22-24] or two of its derivatives, acetyl-beta-methycholine[2,4,8,15] and carbaminoylcholine[6] have been most commonly used as inducing agents. An excellent historical review of the literature on the growth of interest in histamine and acetylcholine has been made by Segal and his co-workers.[11] Certain pertinent data mentioned by them require reiteration at this time because of their relative pertinence to the present study.

Weiss, Robb and Blumgart[25] noted that injected histamine induced dyspnea in asthmatic, bronchitic, emphysematous and cardiac asthma subjects and in a few with congestive failure. Schloesser[20] and Mueller[17] both used histamine as a means of differentiating types of dyspnea. Curry[3] also using histamine found it effected a significant diminution of vital capacity in asthmatic subjects but that normal people were unaffected. Many studies using histamine as an inducing agent for asthma-like attacks have since been done by Segal and his co-workers,[1,2,11] Curry and Lowell[4] more recently by Gaensler,[9] and others.

Since in the present study acetylcholine was used, a brief résumé of the pharmacologic action of the drug as it applies here is in order. Acetylcholine appears to be the chemical mediator of nerve impulses across the synaptic junctions in the entire nervous system, and especially from motor nerve endings to effector organs in the parasympathetic nervous system. This latter action simulates stimulation of the parasympathetic system. In asthma this would involve branches of the vagal nerve. This muscarine-like action can be largely prevented or blocked by an anti-cholinergic drug such as atropine or by cholinesterase, an enzyme which inactivates acetylcholine.

Eppinger and Hess almost fifty years ago advanced the theory that asthma was due to a "pathologic vagotonia." Starr[21] noted that one of his subjects with a history of asthma developed a typical asthmatic attack after administration of acetyl-beta-methylcholine (mecholyl). Villaret and Vallery-Radot[24] reported bronchospasm after injections of mecholyl,

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terminated at will by atropine. Fraser,[8] very interestingly, during bronchoscopy with iodized oil fluoroscopically demonstrated contraction of the smaller bronchi when mecholyl was given. Moll[15] believed the attack produced by mecholyl was indistinguishable from a spontaneous attack of asthma. Moll felt the bronchial nervous system rather than the whole parasympathetic system (as suggested by Eppinger) was involved. Our work with the induction of attacks by small quantities of inhaled aerosolized acetylcholine without production of other actions common to stimulation of the parasympathetic system as a whole, lends weight to this view. But whether previous lung damage resulting in bronchial sensitivity to acetylcholine is a necessary prerequisite is still a moot question. Needless to say, despite the simulation of asthma by use of acetylcholine or its derivatives, its role in the production of bronchial asthma must for the present remain an enigma. It continues, however, to be useful in the study of asthma.

Curry and Lowell[4] and Segal and his collaborators[1,2,11] among others, have shown that mecholyl is capable of inducing asthma-like attacks in subjects with history of asthma and fails to do so in normal subjects. This was usually demonstrated objectively by a marked diminution of the vital capacity. Herxheimer[10] demonstrated the same thing with acetylcholine. Panzani[18] tried to induce bronchial obstruction for diagnostic purposes in normal and allergic subjects by administering a 1 per cent aerosolized solution of acetylcholine. Vital capacity and maximal utilizable volume were reduced in the asthmatic patients after they had inhaled the aerosol for one to three minutes.

Segal and his co-workers[11] felt the induction of bronchospasm could be a useful technique in testing the protective action, against such induced spasm, of various bronchodilator drugs. They[1] showed that atropine and scopolamine would protect against attacks induced by mecholyl but not against attacks induced by histamine, and interestingly when these anticholinergic agents were given by aerosol they protected better against bronchospastic agents given by aerosol than when given by vein. They did not mention the efficacy of protection of parenterally-given anticholingeric drugs against aerosolized bronchospastic agents. Lowell and Schiller[12-14,19] have conducted numerous experiments on asthmatic patients inducing attacks with histamine, pollens, mecholyl or allergens. Significant diminutions of the vital capacity of these patients occurred during these attacks and, since they correlated well with clinical symptoms, appeared to be reliable indices of pulmonary function in evaluating the efficacy of bronchodilator drugs.

In one experiment[19] they tested aminophylline, epinephrine, atropine, and tripelennamine hydrochloride for relative effectiveness in preventing or restoring impaired vital capacity after inhalation of pollen. Aminophyllin proved to be the most protective drug, while epinephrine was effective to a lesser extent but neither tripelennamine hydrocloride nor atropine was

effective as a protective agent. The drugs demonstrated approximately the same order of effectiveness in restoring vital capacity after the induced attack. It is noteworthy that the anticholinergic agents were demonstrated to protect against mecholyl but not against histamine, and whereas aminophylline and epinephrine protected against allergen-induced attacks, an antihistaminic drug and an anticholinergic drug did not. This suggests several possible sites for the action of the various agents used to induce bronchial obstruction. Presumptively these same sites may be the selective targets for the action of the different types of bronchodilator drugs used.

The present study was undertaken to confirm the reliability of ventilatory function tests of aerosolized acetylcholine-induced bronchial obstruction and to compare the effectiveness of four agents (three, having different modes of action) in restoring or preventing decreased vital capacity and maximal breathing capacity resulting therefrom. We tested two recognized anti-asthmatic agents, epinephrine and aminophylline, and two newer drugs, diphemanil methylsulfate and hydroxypropyl theophylline.

Diphemanil methylsulfate is a quaternary ammonium compound with a marked anticholinergic effect. Dann and his colleagues[5] compared its efficacy in relieving acute asthmatic attacks, with epinephrine, ephedrine, and aminophylline. Measurements of breathing capacity showed that the anticholinergic drug was satisfactory in a large percentage of the cases and worked as well as the other agents. Frank and MacLaren[7] found that it was as effective clinically as epinephrine when given subcutaneously in an acute attack but was not suitable for use in chronic asthmatic patients when administered orally. This is noteworthy since atropine, the classic anticholinergic drug studied by most investigators, has proved useless clinically.

Hydroxypropyl theophylline is an experimental drug which acts similarly to aminophylline but is believed to provoke fewer side effects.

METHOD

Eighteen patients with chronic asthma were selected for this study. Before administering any drugs and before each experiment they were tested for three-second vital capacity and maximum breathing capacity (hereafter called V.C. and M.B.C.) with a 13.5-liter Collins respirometer. (Twenty-nine normal subjects were used as base controls and as controls in a few experiments.)

Pretreatment individual variations were determined first in order to assess the significance of post-treatment values; variations in V.C. in the same patient ranged between 0.8 per cent and 8.6 per cent (group mean average, 4.3 per cent) and M.B.C. values ranged between zero and 12.5 per cent (group mean average, 5.9 per cent).

The means for the asthmatic patients ranged between 35.4 and 82.5 per cent of predicted normal values for V.C.[27] and between 14.4 and

TABLE I. PRETREATMENT RESPIRATORY FUNCTION IN SIXTEEN CHRONIC ASTHMATIC SUBJECTS

Age	Sex	Associated Pathology Present	Allergic Sensitivity	Baseline Values			
				V.C., in Liters	Per Cent* of Predicted Normal	M.B.C., in Liters	Per Cent† of Predicted Normal
23	F	None	Marked dust, slight pollens	2.25	74.5	61.6	57.1
43	F	None	Moderate dust and pollens	2.6	77.8	31.0	30.4
71	F	Cardiovascular disease	Marked dust, moderate pollens	1.56	50.9	30.8	53.7
58	M	None	Marked pollens and dust	2.75	62.9	74.8	62.5
62	F	Mild emphysema	Moderate pollens	2.0	54.9	30.8	32.5
48	F	None	Marked pollens and dust	1.9	49.2	28.6	25.0
52	M	None	Marked pollens and dust	3.55	64.5	63.8	40.8
59	M	Moderate emphysema	None	1.4	35.4	17.6	25.1
24	F	Bronchiectasis	Marked dust, moderate pollens	2.0	69.4	46.2	45.2
19	F	Mild emphysema	Slight pollens	1.8	64.4	33.0	34.0
70	F	Marked emphysema	None	1.2	46.1	8.8	14.4
60	F	None	Marked pollens	1.7	55.5	39.6	48.8
56	F	Mild emphysema	None	1.75	57.2	26.4	24.4
29	F	None	Marked dust, moderate pollens	2.35	76.8	44.0	43.4
26	F	None	Marked dust, moderate pollens	3.05	82.5	44.0	45.2
23	F	None	Marked dust, moderate pollens	2.8	79.2	48.4	47.3

*After formula of West[27]
†After formula of Motley[16]

62.5 per cent of predicted normal values for M.B.C.[16] The mean pretreatment values, age, sex, and associated pathology of each patient are shown in Table I.

We then attempted to induce bronchial obstruction with acetylcholine. A 50 per cent solution was prepared freshly each month as an aerosol. We administered the aerosol by inserting the end of a vaponephrin type nebulizer in the patient's mouth and squeezing the bulb at intervals of twenty seconds, four times in all. This usually induced much coughing (in the asthmatic subjects) independently of dyspnea. The V.C. and M.B.C. were tested one or two minutes later. After fifty-seven series of tests on the group we found that acetylcholine invariably effected a reduction in the V.C. and in most instances (forty-eight tests) the M.B.C. also.

The average reduction in V.C. induced by acetylcholine was 47.8 per per cent; the average reduction in M.B.C. was 39.2 per cent. These represent baselines in evaluating the effects of various agents on acetylcholine-induced bronchial obstruction in these chronic asthmatic patients. (In twenty-nine normal subjects acetylcholine caused an average reduction in V.C. of only 3.3 per cent and the M.B.C. *rose* an average of 11.2 per cent.)

We then attempted to reduce or relieve acetylcholine-induced bronchial obstruction in fifteen of our patients. We tested the therapeutic effect of 15 mg diphemanil methylsulfate* subcutaneously, 0.3 mg epinephrine subcutaneously, 500 mg aminophylline intravenously, and 200 mg

*Diphemanil methylsulfate (Prantal) used in this experiment was provided by the Division of Clinical Research of the Schering Corporation, Bloomfield, New Jersey.

hydroxypropyl theophylline† intravenously administered after acetylcholine. Five minutes after each of these drugs was injected the V.C. and M.B.C. in each patient was again tested.

The same agents were tested for their prophylactic effect, except that 25 mg diphemanil methylsulfate and 0.5 mg epinephrine were used in

TABLE II. THERAPEUTIC EFFECTS

Drug and Dosage After Acetylcholine	Variations Following Administration*	
	V.C., in Per Cent	M.B.C., in Per Cent
Aminophylline 500 mg	+29.0	+44.1
Epinephrine 0.3 mg	+28.7	+27.6
Diphemanil methylsulfate 15 mg	+30.4	+37.6
Hydroxypropyl theophylline 200 mg	+10.6	+ 3.9

*Represents degree of improvement from the previously depressed level in ventilatory function induced by acetylcholine.

place of the smaller amounts. V.C. and M.B.C. tests were performed on each patient, then the drugs were injected and five minutes later, the patients received the acetylcholine and were again tested one minute later.

We also wished to determine if two of the drugs (diphemanil methysulfate—the anticholinergic drug and epinephrine—the adrenergic drug) would operate synergistically, if either one had failed to return the ventilatory function to pre-acetylcholine values. Therefore, we tested nine patients before and after administration of acetylcholine and after injection of 0.3 mg epinephrine; ten minutes later 15 mg diphemanil methylsulfate was administered and the patients were retested. Reciprocal experiments, using diphemanil methysulfate before epinephrine, were also performed.

RESULTS*

The diminished V.C. and M.B.C. following administration of aerosolized acetylcholine was improved by injections of aminophylline, epinephrine, or diphemanil methylsulfate; the degree of improvement was least with epinephrine.

Although the experimental drug hydroxypropyl theophylline did not improve ventilatory function values in asthmatic subjects as much as the other three agents, it did relieve the acutely-induced dyspnea and wheezing considerably. Also, this drug was injected as rapidly as possible without side effects such as burning, syncope, nausea, emesis, or palpitation. (Table II) (In nine normal subjects who received acetylcholine, diphemanil methylsulfate produced an improvement in the V.C. of 3.8 per cent and in M.B.C. of 2.5 per cent; this parallels the smaller reduction

†An experimental drug provided by the Schering Corporation.

*Expressed as mean averages among all patients tested in each experiment.

in ventilatory functions values provoked by acetylcholine in normal as opposed to asthmatic subjects.)

Neither aminophylline nor hydroxypropyl theophylline acted prophylactically in acetylcholine-induced respiratory depression; the values were not significantly different from those which occurred when acetylcholine

TABLE III. PROPHYLACTIC EFFECTS

Drug and Dosage Before Acetylcholine	Variations Following Acetylcholine*	
	V.C., in Per Cent	M.B.C., in Per Cent
Aminophylline 500 mg	−26.9	−44.0
Epinephrine 0.5 mg	−16.2	−14.7
Diphemanil methylsulfate 25 mg	− 5.1	− 8.4
Hydroxypropyl theophylline 200 mg	−30.1	−27.0

*Represents the depression of the level in ventilatory function induced by acetylcholine after administration of prophylactic drugs.

was given without benefit of the protecting drugs. Epinephrine offered significant protection. The reduction in V.C. and M.B.C. values following acetylcholine was less than half of what would be expected in asthmatic subjects. Diphemanil methylsulfate was the most protective (approximately 75 per cent) of the agents tested (Table III).

In the experiments to determine synergism it was found that diphemanil methylsulfate injected after epinephrine induced an improvement of 11.9 per cent in the V.C. and 11.3 per cent in the M.B.C. above the improvement produced by the latter drug alone. In the reciprocal experiments epinephrine injected after diphemanil methylsulfate produced an additional rise of 26.7 per cent in the V.C. and 41.6 per cent in the M.B.C.

DISCUSSION

Induction of asthmatic attacks with acetylcholine, and subsequent measurements of ventilatory function, is a simple method used by many investigators for comparing agents purportedly useful in asthma. This may also be a useful technique for studying some phases of the pathophysiology of asthma.[1,2,4,6,11,19,23] The fact that the amount of acetylcholine delivered or absorbed cannot be measured precisely does not seem to impair the validity of the results. After a variety of trials the present method was adopted. It is simple and readily applied. Acetylcholine administered in a 50 per cent aerosolized solution provokes significant bronchial obstruction quickly, as evidenced by markedly diminished values in tests of vital capacity and maximum breating capacity, in chronic asthmatic subjects during the nondyspneic state. Segal found that mecholyl injected intravenously induced marked depression of the vital capacity starting within thirty seconds, and usually returning to normal by the end of eight minutes. Employing the aerosolized technique we noted that the dyspnea induced tended to persist unless relieved—the greater the degree of dyspnea induced, the longer it tended to persist.

A diminution of 30 per cent or more in V.C. or M.B.C. usually required an injection of a drug for relief of the dyspnea. The variations which occur are significant when compared with individual pretreatment variations in asthmatic subjects and with acetylcholine-induced variations in normal subjects. This depression of the V.C. and M.B.C. induced by acetylcholine did not occur in non-allergic controls nor in patients with hay fever or allergic rhinitis who did not have a past history of asthma. Two subjects who were diagnosed by a roentgenologist as having emphysema on the basis of x-rays of their chests but who had never had any clinical asthma or exertional dyspnea, plus one additional patient exhibiting emphysema without symptoms of asthma but who had mild exertional dyspnea also failed to show depressed V.C. and M.B.C. values after acetylcholine.

Aminophylline intravenously, epinephrine subcutaneously, diphemanil methylsulfate subcutaneously, and hydroxypropyl theophylline intravenously are able to reverse, in varying degrees, the effect of acetylcholine on the bronchi of asthmatic patients. This corroborates, in part, the work of Schiller and Lowell in pollen-induced bronchial obstruction. Epinephrine and diphemanil methylsulfate can also exert a protective effect against the depressant action of acetylcholine administered subsequently. The theophylline derivatives in our studies offered little or no protection against acetylcholine but Schiller and Lowell found aminophylline protective in allergen-induced asthma. This suggests different sites and possibly modes of action for the agents tested. The site of action of the anticholinergic drug may be neural and thus it can block further parasympathetic activity. It is to be remembered, however, the anticholinergic drug was administered subcutaneously and its site of action might be considered to be the ganglion or post-ganglionic parasympathetic fibres. The acetylcholine was administered by aerosol. Segal[1] (because of the discrepancies he found in the administering of protective agents and mecholyl through the aerosol and intravenous routes) suggested that perhaps drugs administered by these routes reach the motor end plates of the bronchial musculature by different routes. The author has found, however, within limits that the anticholinergic drug used given subcutaneously could completely reverse mild or moderate induced attacks of asthma, despite the different routes used. Severe attacks could not be completely reversed by an anticholinergic drug alone, whereas the addition of an adrenergic drug could complete the reversal. This suggests intercellular retention of acetylcholine at the bronchial muscle level, not neutralized by cholinesterase or blocked by anticholinergic action on the postganglionic fibres, continuing to act on the bronchial musculature until counterbalanced by the adrenergic action. The action of the adrenergic drug is probably at least partially neural; it stimulates the sympathetic system and thus antagonizes the cholinergic action. The theophylline derivatives probably act locally on the bronchial muscle and/or the

mucosa, and this may account for the failure of these drugs in the present studies to protect against acetylcholine. Epinephrine and diphemanil methylsulfate can each enhance the effect of the other in restoring ventilatory function after administration of acetylcholine. This is readily understandable when one considers the selective action of various drugs on the autonomic nervous system.

SUMMARY

Administration of aerosolized acetylcholine markedly diminished vital capacity and maximum breathing capacity in eighteen chronic asthmatic subjects. The therapeutic and prophylactic effect of an anticholinergic drug, an adrenergic drug, and two theophylline derivatives against these acetylcholine-induced attacks of asthma was determined spirometrically.

Diphemanil methylsulfate, aminophylline, epinephrine, and hydroxypropyl theophylline, in that order of effectiveness, improved ventilatory function depressed by acetylcholine. When administered prior to acetylcholine, diphenmanil methylsulfate and epinephrine, but not the theophylline derivatives, protected against a diminution of ventilatory function. Diphemanil methylsulfate and epinephrine can each enhance the action of the other in restoring acetylcholine-depressed breathing capacity.

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SOME LIMITS TO POPULAR SCIENCE

"There are other barriers to popular understanding. Science would be an uninspiring business if it consisted of no more than the collection of new facts and their application for practical ends. These are but the beginning and the rounding off of a complex process. To be manageable, facts have to be marshaled within the limits of general laws, from which in turn new facts may be deduced. Practical applications almost invariably call for the solution of problems scarcely less difficult—and, indeed, often more difficult —than those involved in the original discovery. Many nonmaterial factors also are involved: imagination to see the significance of facts, pleasure from the pursuit of knowledge for its own sake, the satisfaction of the creative impulse. It is surely unduly optimistic to hope that mere clarity of writing will suffice to convey to the layman a proper understanding of the whole complex intermingling of the material and the abstract which constitutes modern science."—Editorial, *Endeavour,* April, 1956.

DEVELOPMENT OF MULTIPLE SENSITIVITIES FROM PRIMARY SENSITIVITY TO NICKEL

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MULTIPLE reactors are common when doing diagnostic patch tests. The particular positive test responsible for the presenting dermatitis can be a difficult decision to reach. A review of this aspect of patch test reactions was a recent project. The presence of nickel sensitivity was taken as the vantage point from which to correlate the information obtained. Guiding the study were painstaking histories, which included a survey of all remedies used for present attacks of dermatitis. This proved of inestimable value when interpreting positive patch tests; a clinical event confirmed by testing. When possible, remedies used for previous episodes were obtained. Prescriptions producing positive tests were traced for composition. Special attention was given any spreading or flare-ups of dermatitis.

The thigh was the testing site in females and the back in males. A doubtful test was redone on a flexor surface of skin like the abdomen. Patients are prone to shy away from second testings. One true positivity to nickel would have been missed if a recheck had not been made. No delayed reactions were seen. Patients were warned to remove the patch if itching or burning developed. The onset time for patch test symptoms tended to be less than twenty-four hours. The Elastoplast strip method has about replaced the use of conventional patches.[1]

Substances on the testing tray were as follows:

Inorganic.—These consisted of potassium chromate 1 per cent aqueous, nickel sulfate 1 per cent aqueous, gold chloride 1 per cent aqueous, mercuric chloride 0.1 per cent aqueous and cobalt sulfate 1 per cent aqueous. Depending upon circumstances, other inorganic substances were tested such as copper sulfate 10 per cent aqueous, cadmium nitrate 1 per cent aqueous, platinum chloride 1 per cent equeous, zinc sulfate 1 per cent aqueous, iridium chloride 1 per cent aqueous, ruthenium chloride 1 per cent aqueous and paladium chloride 1 per cent aqueous.

Organic.—These consisted of merthiolate 0.1 per cent aqueous, formalin 1 per cent aqueous, monobenzyl ether or hydroquinone 1 per cent in petrolatum, mercaptobenzothiazole 1 per cent in petrolatum, tetramethylthiuram monosulfide 1 per cent in petrolatum, paraphenylenediamine 2 per cent in petrolatum, benzocaine 1 per cent in petrolatum, aqueous perfume deodorant, resorcin 1 per cent in petrolatum and epoxy resin 0.1 per cent in

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TABLE I. DEVELOPMENT OF MULTIPLE SENSITIVITIES FROM PRIMARY NICKEL SENSITIVITY

Patient Case	Onset Site	Presenting Location	Duration	Previous Attacks			Effects of Multiple Sensitivity on Etiology of Contact Dermatitis				
				Trivial	Severe	Hospitalized					
INORGANIC SENSITIVITY											
1	Thighs	Thighs	1 year				Nickel				
2	Ears	Ears	9 months				Nickel				
3	Ears	Fingers	6 months	Ears Wrists (5 years)			Nickel				
4	Ears	Ears	1 month				Nickel				
5	Ears	L. Wrist	6 weeks	Ears Wrists (10 years)			Nickel				
6	Ears	Hands	2 months	Hands (3 years)			Nickel				
7	Fingers	Fingers	6 weeks				Nickel (Cr.)				
INORGANIC AND ORGANIC SENSITIVITY											
1	L. Ankle	Generalized	3 months		2	2	Nickel	Mercury	Formalin	Thiosalicylic Acid	Benzocaine
2	L. Wrist	Hands, forearms, neck, face	3 weeks	Many	4	1	Nickel	Parapheny-Lenediamine	Tetramethyl Thiuram Monosulfide		
3	Ears	Hands	1 month		2		Nickel	Organo-Mercurial			
4	Ears	Flexural eczema	2 months		6	2	Nickel	Benzocaine	Surfacaine	Mercresin	Procaine Furacin Merthiolate
5	Ears	Flexural eczema	4 months	Many	2	1	Nickel (Cr.)	Deodorant			
6	L. wrist	Flexural eczema	15 years		Ev. Summer (15 years)	2	Nickel	Chromate	Formalin	Thiosalicylic acid	
7	Ears	Face, neck	1 month		1		Nickel	Mercapto-Benzothiazole			
8	Ears	Face, neck, upper extremities	2 months		6	1	Nickel	Hair dye	Benzocaine	Monobenzyl-ether of Hydroquinone	Mercapto-Benzothiazole
9	Ears	Face, neck, hands, forearms	6 months	Many	10	2	Nickel (Cr.)	Mercury	Perfume		

petrolatum. As special problems arose, the test substances also included occupational contactants, therapeutic agents and various cosmetics. A positive test to merthiolate was usually followed up by a patch test with thiosalicylic acid 0.1 per cent in alcohol.

During 1957 screening patch tests were carried out on 234 office patients. Nickel sensitivity was found in eighteen. Two of the tests were classed as false positive. Two patients previously sensitive to nickel were seen with recurrences of dermatitis. One showed a positive test in 1954 which remained the same on subsequent testing. The other was shown to be sensitive to nickel at the Mayo Clinic in 1932 and remained positive. Thus, a total of sixteen cases comprised the clinical material. Patients sensitive to only inorganic substances were placed in one division, and those showing combined sensitivity, inorganic and organic, were placed in another. The summaries appear in Table I. The presence of nickel sensitivity was the appraisal point for judging clinical manifestations due to single and multiple sensitivities.

Inorganic Sensitivity.—There were seven patients in this group, four females and three males. The ages varied from twenty-four to sixty with four over fifty. The onset site was small, seldom over a centimeter in diameter. In four patients, the site was the same as the presenting location of the dermatitis. The cutaneous reaction was minimal, a few vesicles dotting a dull erythema. If the location of the presenting dermatitis differed from the onset site, the inflammatory response was not very acute. Four cases had had no previous attacks. Three cases had had many previous attacks described as trivial, little more than a transitory rash, or a few itchy spots. One patient showed a concurrent sensitivity to chromate, and this was considered non-specific.[2] Symptoms were not mentioned, or only casually stated. A positive test to nickel was the etiology of the dermatitis. Clinical evidence quickly corroborated this diagnosis.

Combined Sensitivity (Inorganic and Organic).—Nine patients made up this group, six females and three males. The ages were higher, thirty-four to sixty-four. Seven patients were over age forty. The only relation the onset site had to the presenting dermatitis was that it marked the beginning of a long history of skin diseases. The distribution had to be estimated in terms of body area rather than in centimeters. The clinical manifestations were severe, erythrodermia with massive vesiculation. Weeping was common. Bearing this out are the number of hospitalizations. The duration had turned to long periods of cutaneous disability. Four patients, or nearly half of those in this group, had moved from an acute dermatitis to a chronic one characterized by flexural eczema. They could no longer stand environmental stress without developing cutaneous symptoms and signs. The dermatologic events leading up to

the condition of altered skin physiology or the complaint, "I itch when I get hot," are epitomized in Figure 1.

Symptoms were of major concern. Patients talked about them incessantly. Absence of effective means to control them proved their inspira-

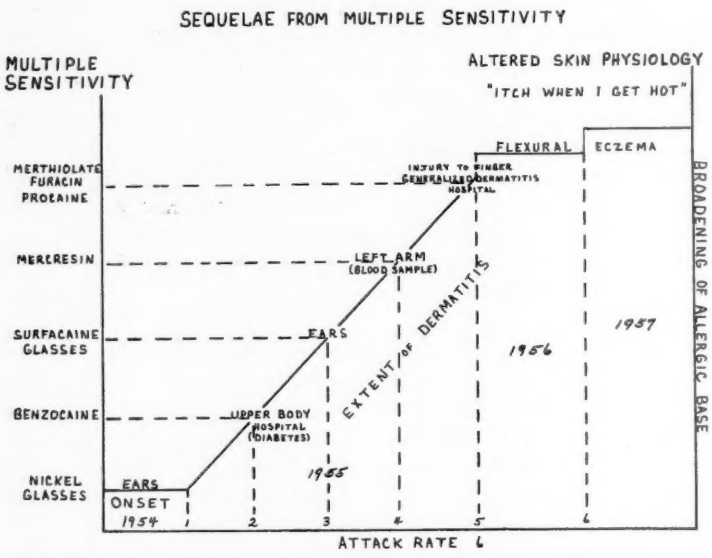

Fig. 1. Case 4 portrays the clinical episodes leading up to the condition of flexural eczema. The diagonal line shows the steady increase in the extent of dermatitis. The attack rate and the corresponding sensitizer are seen to intersect at the diagonal line. A positive patch test confirmed the cause of each attack. Cross sensitization doubtless occurred between the "cain" drugs.[5] The allergic base was broadened by the increase in sensitizers. This patient was free of skin trouble until the temporal bows on his glasses were changed. A nickel dermatitis, trivial in its manifestations, developed into more and more complications. Six organic chemicals and a range of nickel objects can presently erupt his normal-appearing skin. As far as is known, these agents did not do this before. The sequelae of the attacks of dermatitis influenced by the broadening of the allergic base seemed to initiate the onset flexural eczema and the state of altered skin physiology.

tion for visits to many physicians. They were in and out of various hospitals. One patient had been under the care of a psychiatrist, then sought hypnosis, and then went back to another psychiatrist. Four patients had developed habitual manipulations. They continually rubbed and pinched their skin. One was an "opener and squeezer." The skin was palpated for any and all excresences which were promptly picked off and then the area was squeezed. It seemed as if their skin had lost all pain sensation. Uncontrollable pruritus sharply distinguished this group from the inorganic one.

DEVELOPMENT OF MULTIPLE SENSITIVITIES FROM NICKEL SENSITIVITY

Nickel sensitivity stayed single in only seven patients. Another way to say the same thing is that in over half the patients, the etiology of the onset site of dermatitis becomes complicated. Nickel dermatitis, like other disruptions of the cutaneous mantle,[3] proved a good medium for the development of multiple sensitivities or an acquired broadening of the allergic base. All that seems to be required is this. Rub ammoniated mercury into a nickel dermatitis long enough to complete the incubation period for sensitization, and the chances are excellent for the development of mercury sensitivity. If aggravation or spreading of the treated dermatitis occurs, sensitivity is probably dwelling there. Two inorganic substances, nickel and mercury, will now eczematize normal-appearing skin. The basis for the increased attack rate becomes more apparent. Two active allergans widely present in the environment are ready to produce a dermatitis in the person from merely touching the skin. If one of these induces a rash out comes a bottle of red medicine to stop the itching. Vesicles are pricked open to make sure the antiseptic seeps in well. Aggravation, spreading and a snap diagnosis of infection denote the presence of a third sensitizer. The organomercurial may well have contained thiosalicylic acid. If it did, an organic sensitizer is apt to be added to the list. Three substances will now erupt the person's skin. The chances for more attacks have again multiplied. The same or another irritation can be treated with the application of some local anesthetic agents. Easily, another organic sensitizer is added to the list. Now four substances will react with dermatologic signs and symptoms on normal-appearing skin. At about this stage, a still greater danger comes into being—a cross sensitization. Baer[4] reviewed the literature on cross sensitization in allergic eczematous dermatitis. The chemical groups producing cross sensitization among local anesthetic agents were classified on the basis of various reports. Cross sensitizations occurred between certain local anesthetic agents and paraphenylenediamine and between the sulfonamide drugs. The phenomenon also occurs between nitrobenzene and analine and among paraphenylenediamine and azodyes.

EFFECT OF MULTIPLE SENSITIVITIES ON THE DIAGNOSIS OF CONTACT DERMATITIS

Patients having only a sensitivity to nickel presented an easily determined etiology, Table I. Their clinical course was uneventful and, important for this era, inexpensive. Patients having combined sensitivities not only had unfavorable clinical courses, but their etiology had changed and it had become more difficult to detect. Nickel sensitivity merely started things. Clinical events underwent changes in time. As additional attacks of dermatitis develop, the etiology changed with them. Patients 2, 4 and 9 were seen for all their attacks. A positive patch test corro-

borated each. It was hard for Case 9 to believe that perfume would harm anybody. For the remaining cases, histories had to be correlated with patch test results to unfold the etiologic trend. This is by no means finite. If the choice of test substances is broad enough, positive patch tests can disclose the etiology of previous attacks of dermatitis with great accuracy. To prove that a positive patch test is the cause of the present or existing dermatitis, supporting clinical facts are required. This imposes a great responsibility on clinicians. Unless the acumen is kept sharp, positive patch tests might be diagnosing previous dermatoses rather than present ones. The etiology of contact dermatitis is not static or fixed in patients. It shifts with changing exposures to the skin from environmental or therapeutic allergens. When the skin is free of disease in multiple sensitivities, there appears to be no increase in susceptibility to common irritants. A remarkable and unswerving specificity was the rule.

DISCUSSION

In a study of forty cases of nickel sensitivity, Fisher and Shapiro[6] recorded two coincidental sensitivities to mercury, two to paraphenylenediamine, two to benzocaine and one to resorcin. The authors did not state whether these sensitivities had been the cause of any attacks of dermatitis in their patients. Little else on this subject was found in the literature.

Single nickel sensitivity was associated with a minimal extent of dermatities, low attack rates and few, if any, symptoms. Combined sensitivity —inorganic and organic—or multiple sensitivities were associated with acute dermatoses, often extensive in distribution, a high attack rate, severe symptoms and long periods of cutaneous disability. Chronic flexural eczema was the final outcome in four patients. A positive patch test is not diagnostic of a presenting dermatitis unless there is furnished corroborating clinical evidence. The occurrence of multiple sensitivities brings into view all the evils of self-treatment.

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PROBLEMS OF CONTACT DERMATITIS IN THE ATOPIC INDIVIDUAL

With Reference to Neomycin and Ragweed Oil Sensitivity

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CONTACT DERMATITIS is one of the most satisfactory skin conditions to diagnose and treat. Both the doctor and the patient can understand that the skin has been irritated externally by something, and that when the causative agent has been found and eliminated, the dermatitis will disappear. This is true in the non-atopic, *but* in the atopic, a contact dermatitis may be a most perplexing skin disease. If you focus on the problem of chrome dermatitis, a contact dermatitis with a predilection for the atopic, you can visualize the immensity of the clinical challenge. Therefore, in the handling of many cases of contact dermatitis, it is necessary to know if the individual is or is not an atopic.

In this paper we will discuss the practical and useful criteria available to identify the individual as an atopic, exclusive of family and personal history of asthma, hay fever and eczema, and whealing to direct and indirect skin testing and the appearance of the atopic patch test reaction.[14] We shall then apply these criteria to certain cases of contact dermatitis which, because of their clinical aberrations, warrant study from this point of view.

CRITERIA FOR IDENTIFICATION OF THE ATOPIC INDIVIDUAL

Physical.—There is one dependable and easily identifiable, physical characteristic, the extra eyefold. This is sometimes called "Dennie's line"; it is located on the lower eyelid[19] and is a tell-tale that the individual is an atopic. This sign loses some of its value in older people with the appearance of wrinkles.

Physiologic.—There are two physiologic criteria. The first is the so-called "delayed blanch," first reported by Lobitz, where vasoconstriction or

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blanching is noted a few minutes after the intradermal injection of 0.1 ml of a 1:10,000 solution of acetylcholine into a region of involved skin.[16] Blanching from acetylcholine is a marked deviation from the expected pharmacologic reaction of vasodilation or redness. Blanching will occur

TABLE I. PHARMACOLOGIC METHOD OF IDENTIFYING THE ATOPIC
Response to I.D. acetylcholine and topical trafuril.

	Atopic Derm.	Non Atopic Eczema
Acetylcholine	Blanching 50—65%	Erythema 100%
Trafuril	Blanching 85—100%	Blanching--50%

in 50 to 65 per cent of patients with atopic dermatitis. The second criterion is the blanching which occurs fifteen to thirty minutes after the application of an ointment containing a nicotinic acid ester, Trafuril®, to an area of involved skin. Blanching will occur in 85 to 100 per cent of patients with atopic dermatitis. When Trafuril® is applied to normal skin, whealing is occasionally produced (Fig. 1). This reaction occurs only in the atopic individual.

Fig. 1. Wheal reaction to topical Trafuril®.

When blanching is observed, in the first, using acetylcholine, it is found only in atopic dermatitis. In the second, using trafuril, blanching is sometimes observed in patients with non-atopic eczematous disease, but these always give a normal erythematous reaction to acetylcholine.[4,22] The combination of the data obtained from the above two procedures enables one

Fig. 2. Spongiosis and beginning vesiculation around sweat duct unit.

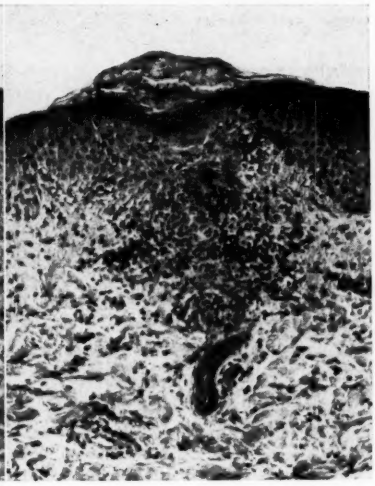

Fig. 3. Parakeratotic crust overlying sweat duct.

to determine with reasonable certainty whether or not a given eczematous disease is atopic dermatitis (Fig. 1).

(c) *Histopathologic.*—We would like to suggest that there is a distinctive histopathologic picture occurring in the skin of atopics after patch testing with certain substances. This histopathologic finding has been fully described by Epstein;[6,7] he did not, however, specifically relate it to the atopic individual. It consists of localized, well-circumscribed intra-epidermal vesiculation or spongiosis. The distinctiveness of this reaction is its periporal location (Fig. 2). Epstein writes, "all of these individual lesions are associated with sweat pores, but appear to be paraductal, the duct finding its way around the vesicle or spongiotic zone." The reaction takes place within hours after patch testing because examination of a biopsy taken at forty-eight hours will demonstrate that many of these periporal lesions are being shed as parakeratotic crusts (Fig. 3).[17]

On occasion, it may be helpful to evaluate one other stigma of the atopic state, the cold pressor test.

The patient is placed in the supine position, with one of his hands in ice water; one minute later, his blood pressure is taken from the opposite arm. The normal or non-atopic diastolic pressure rise over the basal level is not more than 15 mm of mercury. Most atopic individuals will have a hyperreactive type of response with a greater elevation of the diastolic pressure.[10]

No single criterion is invariably present and no single criterion *per se*

is diagnostic of the atopic state. Yet these peculiarities are valid statistically when summed up in identifying the asthma, hay fever and eczema complex.

CLINICAL APPLICATION OF ATOPIC CRITERIA

Those of us specializing in dermatology and allergy are constantly confronted with clinical diseases occurring in the atopic individual. We take complete histories of allergic disorders, and frequently perform skin tests to detect passively transferrable reagins. Although we are all familiar with the pustular reaction from nickel as one of the dependable criteria for the atopic state, we rarely perform this patch test to identify a given individual as atopic.[18]

Certainly the time has come when our routine office procedures should include investigation for physical, physiologic and histopathologic stigmata of atopy. Knowledge is of no value unless applied. As stated, we have been applying these criteria to various cases of contact dermatitis, which, because of their clinical aberrations, warrant study from this point of view. We wish now to discuss specifically the problem of Neomycin and ragweed oil sensitivity.

Neomycin Sensitivity.—This clinical entity has been firmly established by the excellent observations of Stephan Epstein. We are entirely in agreement with his opinions.[7,8,9]

The criteria for identifying atopy were applied to ten cases of contact dermatitis from Neomycin. All of our patients were atopics. A single case will re-emphasize the salient features of contact dermatitis from Neomycin.

CASE PRESENTATION

A woman, aged fifty, was seen because of an eczematous dermatitis of the left flexor arm (Fig. 4). She stated that for several months she had had a dry, itchy dermatitis of this area. Previously, treatment with Neomycin ointment had irritated the dermatitis. Later, the itching was relieved by application of a 2.5 per cent Neocortef® ointment; the dermatitis did not, however, subside. All her treatment was stopped, and within several weeks the original underlying neurodermatitis circumscripta reappeared (Fig. 5). An intradermal skin test of a 1:1,000 solution of neomycin sulfate was positive at forty-eight hours as a 1 cm. papule. A patch test to Neomycin ointment was positive when read at forty-eight hours. It was characterized by multiple small eczematous areas rather than by a confluent eczematous plaque (Fig. 6). Examination of the biopsy from this patch test site revealed dermal changes as well as the distinctive, focal, well circumscribed periporal spongiosis.

Historical, physical and physiologic criteria for atopy were present in this patient.

Other skin diseases complicated by neomycin sensitivity include hand and ear eczema cases. If such a dermatitis, being treated by one of the many available preparations containing neomycin, at first markedly im-

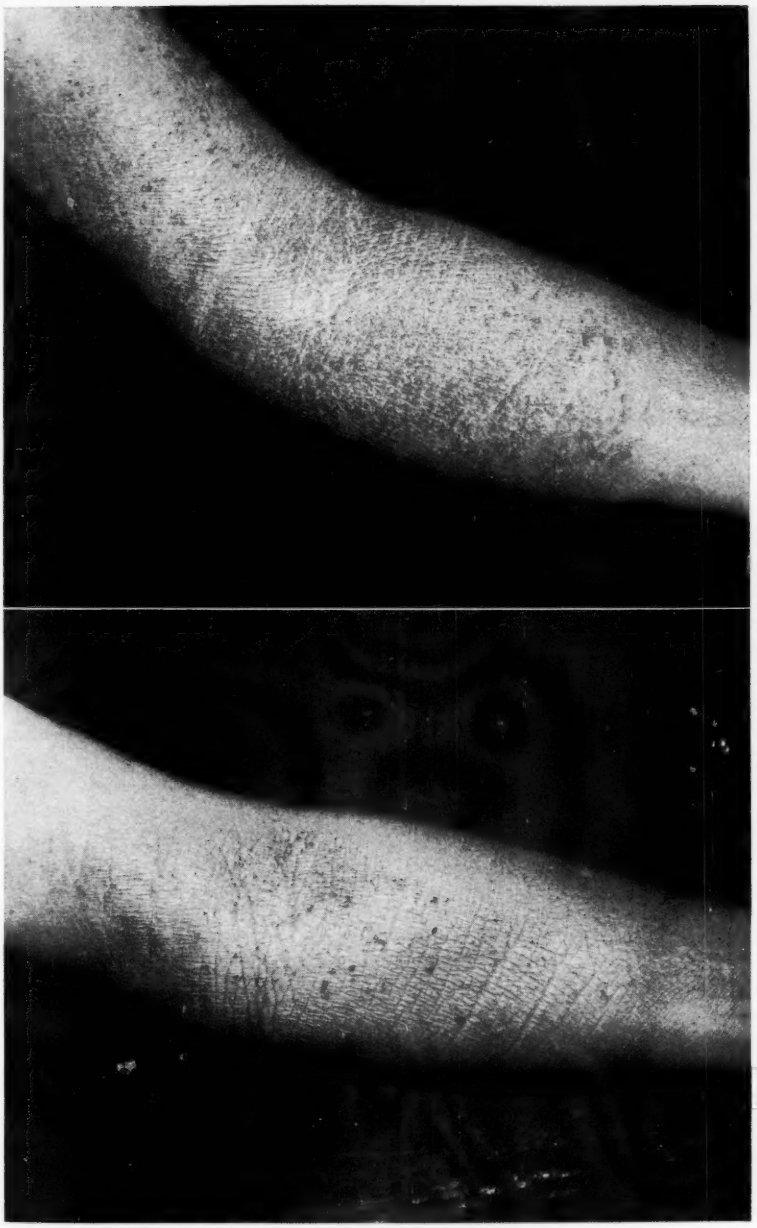

Fig. 4 *(above)*. Eczematous reaction produced by Neomycin.
Fig. 5 *(below)*. Underlying neurodermatitis circumscripta demonstrated when eczematous reaction of Figure 4 disappeared following avoidance of Neomycin.

proves, then either fails to continue improving or gets worse, neomycin sensitivity may be suspected.

This disease will be found to occur predominantly if not exclusively in atopics.

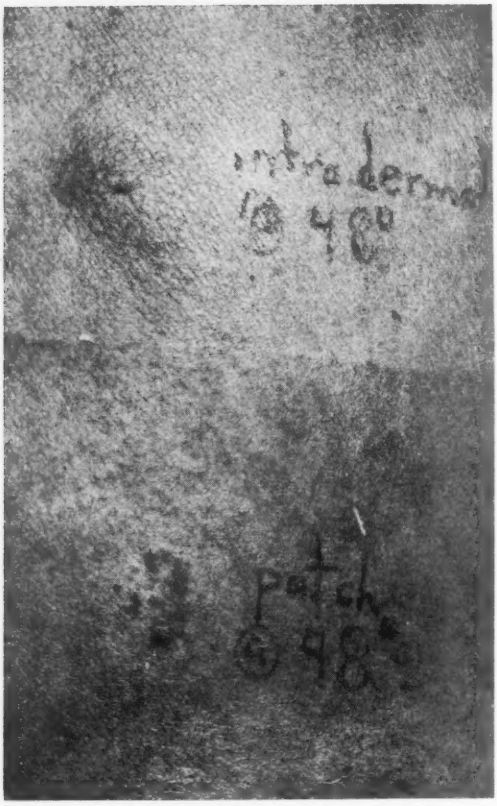

Fig. 6. Positive intradermal and patch test reactions to Neomycin. Note multiple small eczematous areas at patch test site.

Ragweed Oil Sensitivity.—Contact dermatitis from ragweed oil has certain aberrations which suggest a strong predilection for a specific type of individual. The usual person with this disease is a man over the age of forty. The disease is characterized by chronicity and lichenification; this latter morphologic alteration is said to occur predominantly in the atopic individual.[26]

The present concept of contact dermatitis from ragweed oil is that it is not related in any way to atopy. It has been emphasized that the

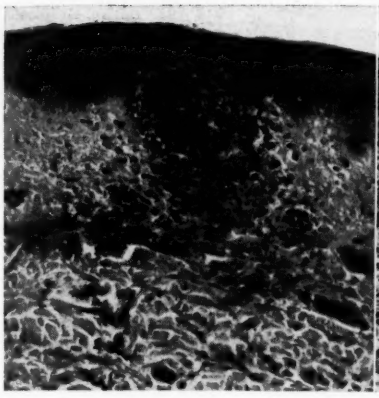

Fig. 7. Biopsy of ragweed oil patch test showing early minimal spongiosis around sweat duct unit.

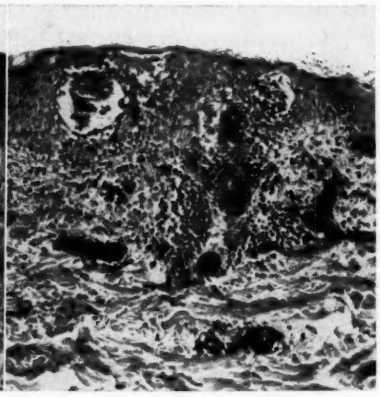

Fig. 8. Biopsy of ragweed oil patch test showing a marked reaction of vesiculation around epidermal sweat duct.

majority of these patients neither have atopic dermatitis nor evidence of asthma or hay fever.[11] It even has been stated that atopic individuals rarely get ragweed oil contact dermatitis, suggesting that these individuals are in some way immune to this disease.[5] This separation of this particular type of contact dermatitis from atopy took place in 1931 when Brown, Milford and Coca found that it was the oily fraction of the ragweed pollen which was the sensitizing agent.[1] They stated at that time that ragweed contact dermatitis was not related to atopy. Brunsting originally agreed and stated that there was no more than a casual relationship between contact dermatitis from ragweed oil and the atopic state.[2] In a later report, however, he noted more than a casual relationship between the two, in that over 20 per cent of his patients had either a positive family history or past history for atopy.[3]

Of great importance was the finding of a wheal reaction to ragweed pollen in over 10 per cent of these patients; six positive in twenty-eight tested by Brunsting.[3] It should be recalled that before the causative ragweed oil was implicated, Hannah[13] and Sutton[24] made their original diagnosis not only because of the seasonal incidence but also on the finding of wheal reactions to ragweed pollen. Pascher, Sulzberger[20] and Gay [12] noted this. Gay, in addition, stated, "There is a reasonable doubt that every case of ragweed dermatitis is purely a contact dermatitis."[12] We performed intradermal skin tests to ragweed pollen in thirty patients having contact dermatitis chosen at random and found one positive wheal reaction.

All six of our patients with contact dermatitis from ragweed oil were identified as atopic individuals. Two of the six had an immediate wheal reaction to intradermal ragweed pollen. One patient, in addition, had a

history of allergic rhinitis during the ragweed season but had a negative wheal reaction to intradermal ragweed pollen. The skin test site was positive, however, at forty-eight hours.

Histologic examination of the positive ragweed oil patch test sites revealed the unusual epidermal finding of spongiosis and vesiculation around the sweat duct unit (Figs. 7 and 8). This is the first time, to the best of our knowledge, that this distinctive epidermal change has been associated with ragweed oil contact dermatitis.

DISCUSSION

Epstein considers Neomycin sensitivity an example of dermal contact dermatitis. Many of his patients had a negative patch test to Neomycin, but all had a positive intradermal skin test.[7,8,9] In most of our cases of contact dermatitis from Neomycin, the patch test was positive. Some of these, however, were not clinically evident as being positive until twenty-four hours after the patch was removed, and even then only as a small cluster of minute papules. The intradermal test with Neomycin in our patients was always positive at forty-eight hours and was easier to read than the patch test. This discrepancy in response between patch and intradermal skin testing has also been noted in certain cases of contact dermatitis from nickel and chrome.[1] Vesiculation and spongiosis around the sweat duct units are found in positive patch tests to nickel, chrome, Neomycin and ragweed oil: from our experience, this is found solely in the atopic. (Even the atopic pustular reaction to a patch test with nickel consists of an intra-epidermal pustule related to the sweat duct.)[25]

Taking nickel as an example, it is known that this material, when applied to the skin, accumulates preferentially in and around the sweat ducts.[25] Chrome, Neomycin and ragweed oil may be similar.

Strauss and Kligman have succeeded in converting an experimental contact dermatitis from poison ivy to a chronic neurodermatitis by exposing the experimental subjects on whom the contact dermatitis was produced to antigens to which whealing occurred.[23] They were successful in using inhalant, surface application, and injection routes for the specific whealing antigens. We should suggest that a parallel situation exists in the maintenance of contact dermatitis to ragweed oil and Neomycin. The antigen, fixed in its particular location, is influenced in some way by a reaginic antigen-antibody combination within the body to produce the aberrant form of contact dermatitis with which we are clinically familiar.

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SCIENCE

"The general aim of science is to progress towards, and ultimately achieve, such theories. We can never say that any theory is final or corresponds to absolute truth, because at any moment new facts may be discovered and compel us to abandon it."—JAMES JEANS, *New Background of Science*, Cambridge University Press, 1934.

PROCHLORPERAZINE AS AN AID IN THE TREATMENT OF BRONCHIAL ASTHMA

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BRONCHIAL ASTHMA has always presented a difficult problem of management. Treatment is likely to be protracted since the etiology often involves a complex of allergic, infective, and psychic factors. At the same time, the distress of attacks tends to create or aggravate anxiety and depression. This cyclic effect that develops when the distress of attacks is not allayed by traditional treatment tends further to aggravate symptoms. Typically, attacks occur more frequently at night when the patient is by himself—most at the mercy of his fears and depression.

It is thus important to give sustained symptomatic treatment both to counteract asthmatic manifestations and to alleviate attendant anxieties. Sympathomimetic drugs have sometimes the disadvantage of enhancing excitation and nervousness.[1] The concomitant use of mild sedatives may increase depression and is ineffective for extreme anxiety or irritability. Narcotics, necessary in special cases, have been found to aggravate the paroxysms of asthma by retarding the cough reflex. Corticosteroid therapy has proved its worth beyond question, but its use, too, is accompanied by limitations and it is extremely important to establish maintenance dosages at the lowest possible level capable of insuring comfort and eliminating symptoms.

In view of these limitations of the usual therapy and the complicating effect of psychic distress in asthmatic conditions, we were prompted to institute a regimen employing a recently introduced tranquilizing drug, prochlorperazine,* in addition to specific asthmatic medications.

Animal pharmacological studies[2] have shown prochlorperazine to be quite potent in blocking conditioned escape response in rats (twice as potent as chlorpromazine), indicative of tranquilizing activity in human beings, and to be a potent antiemetic (six times as potent as chlorpromazine). The drug appears to have a wide margin of safety.

Preliminary clinical reports have borne out these laboratory indications of safety and efficacy. Wennersten[3] and Vischer[4] report that 62 per cent and 55 per cent of patients, respectively, gained prompt, marked relief from pain or psychosomatic complaints while on relatively low dosages of prochlorperazine. Less than 5 per cent in each study experienced no appreciable symptomatic relief. Side effects were infrequent and limited to mild drowsiness and dizziness, disappearing when the drug was discontinued. No blood dyscrasias or jaundice were encountered.

*Compazine,® Smith, Kline & French Laboratories, Philadelphia, Pennsylvania.

Vischer reports that confusion and depression "disappeared dramatically" in many patients.

The fact that prochlorperazine had proved effective in low dosages for treating mild and moderate emotional disturbances, without causing or aggravating depression, made the drug potentially desirable for our purposes. We were interested in gauging its effectiveness in the following areas: (a) in relieving the anxiety and depression attendant upon asthmatic manifestations, (b) in sustaining emotional adjustment when changes in environment were necessary, (c) in possibly helping to establish lower, safer therapeutic levels of steroids when they are necessary and (d) in determining the incidence and severity of side effects.

MATERIAL AND METHOD

Twenty-six pediatric patients hospitalized for bronchial asthma and six out-patients (four adults, two children) made up the study group. The children ranged in age from six to sixteen years; the adults, from forty-eight to sixty-one years. Nineteen of the total were male; thirteen, female. Most of the asthmatic conditions were chronic. Over half the patients had been afflicted from infancy, only seven for less than six years.

For all patients, prochlorperazine was prescribed specifically for asthma or for closely associated symptoms of emotional stress. In most cases, depending upon need, established medications for bronchial asthma (sympathomimetic amines, aminophylline, and iodides) were used concomitantly with prochlorperazine. Corticosteroids were employed for approximately one-half the patients. Prochlorperazine was administered in divided dosages totaling between 10 mg and 30 mg daily. Most frequently, 15 mg was the daily dosage.

Each patient's progress was recorded on a case form, and the results of prochlorperazine therapy were rated as "Good," "Fair," or "Poor," according to the following criteria:

Good: marked improvement in terms of decreased frequency and severity of asthmatic attacks and in terms of emotional adjustment to condition; 50 to 100 per cent reduction in steroid therapy when it was used.

Fair: definite but limited improvement in asthmatic manifestations and emotional factors; appreciable reduction in therapeutic dosage level of steroid hormones.

Poor: No noticeable change in psychic symptoms or in frequency of asthmatic attacks; no effect on steroid treatment.

The duration of prochlorperazine treatment varied from four weeks to over four months, the average being about nine weeks.

RESULTS

Results were "Good" for eighteen patients (56 per cent), "Fair" for eight patients (25 per cent), "Poor" for six patients (19 per cent). For five patients no concomitant medication was required. Sixteen required

steroid therapy. For all but two of these, prochlorperazine made possible substantial reductions of effective dosages without triggering anxieties or depression. Dosages were reduced usually to one-half or one-third of those formerly required; steroid agents were withdrawn completely for three patients. No side effects attributable to prochlorperazine were observed, and in no instance was the primary condition of bronchial asthma adversely affected. In one pediatric patient, atopic dermatitis, which had accompanied the asthmatic condition, completely subsided during treatment.

TYPICAL CASE REPORTS

Case 1.—J. B., aged eleven years. This girl suffered from bronchial asthma recurrent from infancy. Manifestations of asthma had become largely psychogenic. Five months after admission the patient was started on steroid therapy (prednisolone, 7.5 mg daily, which was gradually reduced to 2.5 mg daily). Prochlorperazine was given concurrently, 5 mg t.i.d. Asthma did not recur during the withdrawal of steroid hormones. The child's behavior improved noticeably; her shy, withdrawn habits were replaced by a cheerful, outgoing interest in her environment. Recently, there have been attacks of asthma but much less severe than formerly. Results of treatment with prochlorperazine: Good.

Case 2.—S. A., aged eight years. This girl was seen in the outpatient clinic for her bronchial asthma of six years' duration. Conventional therapy was ineffective for six months, after which prochlorperazine, 5 mg t.i.d., was added to the regimen. We noted immediate improvement, which was sustained when, in the course of treatment, the patient was separated from her home environment and placed in a foster home. She is now in her own home again with no indications of asthma. Results of treatment with prochlorperazine: Good.

Case 3.—J. E., aged sixty-one years, male, had suffered from bronchial asthma since infancy. Attacks had become severe in the three months prior to his first visit to our office. At that time he had been receiving heavy dosages of prednisolone. Treatment with prochlorperazine was begun and made possible a reduction of steroid therapy; however, there were some attacks of asthma of increased severity which necessitated temporarily higher steroid hormone doses.

The patient is now off steroid therapy but is continuing prochlorperazine, 5 mg t.i.d., and is doing very well. The disorder was diagnosed as psychogenic. The patient came to realize this, and with the help of the tranquilizing drug, was able to weather some difficult and trying times. Results of treatment with prochlorperazine: Good.

Case 4.—J. J., aged fourteen years, is a boy with a history of bronchial asthma for six to seven years. Chlorpromazine had been employed to alleviate apprehension but was ineffective in controlling asthma. Prochlorperazine by itself was somewhat more effective, but the best control was secured with prednisolone (10 mg daily) in combination with prochlorperazine (5 mg t.i.d.). This was a rather small amount of prednisolone to have achieved such satisfactory results. Reduction of the steroid hormone dosage is being gradually effected with no increase in frequency or severity of attacks of asthma. Results of treatment with prochlorperazine: Fair.

Case 5.—M. P., a girl aged fourteen years, is a chronic asthmatic patient with a heavy psychic overlay who suffers from numerous acute asthmatic episodes, many of which have required that she be hospitalized. Relatively high dosages of steroid hormones had been given her for about six months, at which time prochlorperazine, 5 mg t.i.d., was added to the therapeutic regimen. Almost six months of the combined therapies have resulted in substantially the same results as the steroids therapy alone. Results of treatment with prochlorperazine: Poor.

COMMENT

The first three patient cases typify the kind of help prochlorperazine furnished when it did help; it served to check attacks of asthma during emotionally-critical periods; it enabled us to reduce steroid hormone dosages to safer levels without impairing their therapeutic effect and without aggravating emotional stress as often happens in the immediate post-steroid period when the euporia that may accompany steroid therapy is absent. It allayed background anxieties, thereby helping to clarify the etiologic picture and induce in the patient a realistic, hence therapeutic, attitude towards his condition.

Case 4 exemplifies the "fair" results. The effectiveness here of prochlorperazine in combination with steroid hormones in controlling seizures is by itself sufficient to justify continued use of the drug. However, since psychic factors did not disappear we considered the results only fair.

Case 5 represents the "poor" results. Emotional factors were clearly present but were not alleviated by the tranquilizing medication, nor did it have any favorable effect on steroid hormone treatment.

In ten of the institutionalized patients, asthma was inactive or very mild during the early period of hospitalization and medication was limited to tranquilizing drugs. Only two of these patients subsequently developed severe asthmatic attacks, the cause in each instance being the anxiety associated with imminent departure from the institution. One child later responded well to renewed prochlorperazine therapy. For most of the ten, prochlorperazine was undoubtedly an important factor in holding off symptoms of asthma, since all patients suffered from asthma of many years' standing.

DISCUSSION

Children afflicted with bronchial asthma pose a singular problem, especially when the extent of the disease necessitates separation from the environment of home. Many such children come from homes which may be described as disturbing, unhappy, or tense. Marital difficulties of parents and overcrowded housing conditions are typical underlying problems. Often the hostility of the parents takes the subtle form of rejection. Thus, with children suffering from intractable asthma, with it is emotional factors directly relating to home and family that are largely responsible for remission after the children enter the hospital and for exacerbations when they go home. We usually found prochlorperazine

to be very helpful in transitional situations by sustaining a calm adjustment and inhibiting attacks of asthma during the first weeks of institutionalization or at other times when anxiety was likely to occur, as, for example, in the days surrounding visits of parents, or during preparations for returning home, or while facing the imminent prospect of returning to school after many months' absence.

We have seen that prochlorperazine was effective in over 80 per cent of reported cases as an adjunct to steroid hormone therapy. Derbes,[5] Thorn[6] and others have referred to the frequent untoward effect in steroid hormone therapy of psychic changes "which usually trend toward euphoria or even hypomania." Thorn feels that some degree of euphoria may be attributed to the striking relief of pain or disability but that it may also be due to the direct effect of adrenal hormones on the central nervous system. In any event, the withdrawal of steroids can have serious adverse effects; the euphoria that had attended their use gives way to an emotional letdown often characterized by apprehension, anxiety, and depression. Brown[7] points out that the patient with bronchial asthma is especially susceptible to intercurrent infection and stress situations in the five to ten days after ceasing steroid treatment. Prochlorperazine was an aid in bridging this poststeroid period, by helping to sustain the patient's emotional adjustment so that it was not necessary to re-institute high levels of steroid therapy.

The fact that no side effects accompanied the tranquilizing action of the drug makes it desirable over the sedatives ordinarily employed to ease the discomforts of bronchial asthma. The latter agents, when potent enough to sedate effectively, often have a depressive result and sometimes impede the cough reflex of asthmatic attacks, thus causing dangerous congestion of bronchial passages.[1] None of these manifestations developed from prochlorperazine therapy. Rather, we noted in a number of patients the gradual emergence of a "therapeutic" attitude concerning their condition and adjustment to environment. For example, the indefinite complaints and anxieties of several older children gave way to a realistic concern about school deficiencies brought on by so many missed classes due to hospitalization.

Thus, we believe that prochloperazine is a valuable aid in the treatment of bronchial asthma, principally indicated where mental and emotional problems are involved. The general effect for the patients discussed in this paper has been a decrease in the frequency and severity of asthmatic symptoms. In addition, we have noted in most patients a definite lessening of anxiety and tension without concomitant drowsiness or depression.

SUMMARY

1. Twenty-six hospitalized pediatric patients and six out-patients all suffering from long-standing, recurrent bronchial asthma were treated with prochlorperazine along with specific asthmatic therapy.

2. Prochlorperazine was administered in daily dosages of between 10 mg and 30 mg for periods ranging from four weeks to over four months.

3. Fifty-six per cent of the patients showed marked improvement in terms of decreased frequency and severity of asthmatic attacks, control of emotional factors, and reduced need of corticosteroids when they were part of the treatment; 25 per cent showed some improvement; 19 per cent were relatively unaffected by prochlorperazine.

4. No side effects were observed, and in no instance was the primary condition of bronchial asthma adversely affected.

5. In almost all instances where steroid hormones were employed, the concomitant use of prochlorperazine made it possible to eventually eliminate them or at least reduce dosages to safer levels without impairing the steroids' efficacy. Prochlorperazine also appeared effective in sustaining emotional adjustment in the post-steroid period.

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THE GLAMOUR OF STATISTICS

"Such is the glamour of statistics, that the oncoming generation too readily overlook this distinction. Procedures which might be defensible as screening devices thus become an encouragement to evade reality and an excuse for curbing curiosity about fundamental issues. In short, a calculus of uncertainty is becoming the creed of a cult which disdains to press forward to greater certainty when certainty constitutes a useful addition to the enduring corpus of scientific knowledge. In part, the appeal of its doctrine is due to the prestige which mathematics, however irrelevant, confers on those who use it as a tool of interpretation. In part, it results from a failure to distinguish between the permanent factual bricks continually added to the ever-growing edifice of scientific knowledge and a temporary scaffolding of metaphors which the builders discard at their own convenience."—LANCELOT HOGBEN, *Statistical Theory*, W. W. Norton & Company, New York.

Progress in Allergy

DERMATOLOGIC ALLERGY V

Critique and Review of the Recent Literature

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(Continued from the January-February issue)

Phenylindanedione.—East and Beamish[64] reported the case of a sixty-four-year-old man with a three-day history of recurrent angina and electrocardiographic evidence of coronary disease. He was given heparin (50 mg) intravenously every four hours for twenty-four hours and then started on phenylindanedione (50 mg) in divided doses. On the fifteenth day a generalized, diffuse, erythematous, macular eruption developed. This did not respond to local applications or to antihistamines. Twelve days later fever developed and the patient soon became jaundiced. The symptoms regressed with the administration of Meticorten.

Procaine.—In response to a query regarding the treatment of allergic reactions to procaine, it was recommended[190] that one should rely primarily on the early use of epinephrine and, in addition, it was recommended that 7½ grains (0.5 gm) of aminophylline be administered intravenously. Corticotropin, corticoids, or antihistamines should not be solely relied on for controlling a rapidly occurring, explosive, anaphylactic type of reaction. Hormones act too slowly to meet the emergency and antihistamines, even administered intravenously, are inadequate for overcoming a severe anaphylactic reaction.

Pyrazolone.—Halpern and others[102] reported the case of a forty-six-year-old man in whom symptoms of anaphylactic-like shock developed after ingestion of aminopyrine. The results of skin tests with aminopyrine were strongly positive and passive transfers to a nonallergic recipient were regularly successful and strongly positive. Positive reactions were obtained after oral absorption in a nonallergic recipient and the ingestion of a challenging dose. Ten to fifteen minutes after ingestion, the site of injection of the patient's serum was swollen, pruriginous and intensely red. The antibody is rapidly fixed in passive transfer and the reaction reaches almost a maximum in four hours after the intradermal injection of the serum. The antibody is thermolabile and is destroyed by heating for thirty minutes at 58° C. It is likely that the antigen-antibody complex is formed with a chemical substance without any previous conjugation. Aminopyrine acts as a complete antigen. This explains the immediate and urticarial type of reaction to the scratch test. It is believed that the clinical picture was mediated by histamine. The wheal and flare reaction, symptoms of prickling and urticarial blotches, and vascular collapse could be attributed to a release of histamine. In addition, the symptoms produced in this patient by aminopyrine were controlled by antihistaminics. It is

well recognized that attempts to demonstrate the specific antibody in aspirin allergy have failed in almost every case. This is true in most types of drug allergy in the reviewer's experience.

Quinine.—Novy and Lamb[156] reported a nearly universal dermatitis in a thirty-six-year-old man following the ingestion of gin and tonic. The tonic portion of the drink contained quinine water. A history of probable quinine sensitivity on previous occasions was obtained. The palms and soles were covered with bullae which coalesced in places to form large blebs. On soothing local treatment as well as supportive treatment with corticotropin and tripelennamine citrate, he improved so that he could be discharged after six days. About a month later, a patch test was performed, using a 1 per cent solution of quinine bisulfate. After forty-eight hours, the patch test site showed a marked reaction with a large bulla measuring 8 by 8 centimeters. A similar patch test made with quinine water gave negative results, probably because of the minute amount of quinine present. It has been estimated that some quinine water contains 30 mg of quinine per pint.

Streptomycin.—A query is raised in reference to a thirty-year-old man who was treated with streptomycin intramuscularly for six months. Within two or three minutes of an additional injection, severe pulmonary edema, cyanosis, shock, and near syncope suddenly developed. The patient recovered. The consultant[185] stated that in this case an immediate or anaphylactic type of response to streptomycin had developed. Such acute manifestations are not frequently seen in conjunction with streptomycin; the delayed reactions are more common. A similar case was reported by Rosen in 1948.

Thiamine.—Fahlberg and Dukes[73] noted that approximately 200 cases of allergic or toxic reactions to thiamine have been reported. Reactions have occurred regardless of the route of administration. The molecular weight of thiamine is 337.3; it would not be expected to possess sensitizing capabilities unless spontaneous conjugation with body protein occurred *in vivo*. It was impossible to demonstrate the development of a hypersensitive state toward thiamine hydrochloride in the guinea pig, employing multiple injections of thiamine, thiamine plus adjuvant, or thiamine incubated with normal guinea pig serum. Precipitating and complement-fixing antibodies were not demonstrable with the techniques employed. Several hundreds of cases of untoward reactions to thiamine have been reported. These reactions have included asthma, urticaria, shock and even sudden death; they occur usually after injection of thiamine and often late in a series of treatment with large doses. Many normal persons show an immediate papular response to an intradermal injection of thiamine. Most of these reactions have been caused by intolerance or the pharmacological action of thiamine upon the autonomic nervous system, since thiamine normally accentuates the various effects of acetylcholine. Allergic eczematous hypersensitivity to thiamine has only rarely been reported. Hjorth[107] reported the case of a seventeen-year-old factory girl who had suffered from eczema in infancy. After four months of work at a pharmaceutical firm where she filled vials with different vitamin preparations, eczema of the fingers and dorsum of the hands and wrists developed. Later perioral eczema developed. During a short absence from work the eczema disappeared, only to recur when she resumed her former occupation. Patch

tests were made with a number of substances. Reactions to thiamine were positive even with a 0.1 per cent dilution. In further testing of this patient, results of patch tests with thiamine were positive as previously and a cross reaction to co-carboxylase was demonstrated. The eczema recurred after ingestion of thiamine (200 mg) and later after an intracutaneous injection of 10 mg of thiamine.

Tranquilizers.—Bernstein and Klotz[19] discussed the allergenicity of tranquilizing drugs. A list of common agents in this category is given. The sensitizing properties of reserpine, chlorpromazine and meprobamate are described in detail. Reserpine may produce skin eruptions, urticaria, nasal congestion, malaise and skin sensitivity in experimental animals. Chlorpromazine may produce dermatitis by ingestion or by contact. Photosensitivity, pruritus, blood dyscrasia, and other systemic reactions have been reported. Meprobamate has been known to produce angioedema, urticaria, erythema, fever and purpura, in addition to certain other systemic side effects. Allergic reactions to meprobamate were observed in eight patients by the authors and in seven other patients reported to the authors by personal communication.

Vaccine (D.P.T.).—Rosenblum[213] reported on unusual reactions to D.P.T. vaccine (diphtheria, tetanus and pertussis) caused by silk antigen. Reports of previous anaphylactic reactions to toxoids are recorded. The history of an eight-year-old boy who was given a booster injection of D.P.T. vaccine-alum precipitate is recorded. The child had been given a booster injection three years previously with no ill effects. Ten minutes after the injection, the child started to cough and wheeze and a generalized urticarial eruption developed. Improvement followed the use of epinephrine and Benadryl intramuscularly. Scratch tests to a number of agents including various vaccines were then made. These tests gave negative results. The child was found, however, to have a decidedly positive reaction to a scratch test for silk. It was established that this particular brand of vaccine is filtered through bolting silk during its manufacture. Scratch tests to an extract of this bolting silk showed a violent positive reaction and a simultaneous constitutional reaction. Passive transfer studies established the presence of a circulating reagin to the silk extract and to the vaccine.

Vaccine (Salk).—Lipman[133] made a clinical and statistical report on the reactions occurring in a group of 3,970 school children who received the first and second injections of Salk poliomyelitis vaccine. One hundred and six children displayed true allergic reactions. In four patients severe allergic reactions occurred (with urticaria or angioedema) and in two, wheezing and conjunctival irritation were noted. The reaction in the vaccinated children might be caused by the penicillin, but allergic children should not be denied the protection of the Salk vaccine. A small amount of antihistaminic may be added to the vaccine in carefully screened allergic patients and more use could be made of fractional doses in selected patients. Stroud and others[241] reported cutaneous eruptions after the use of Salk poliomyelitis vaccine in mass vaccination of children and adults in Cleveland. Twelve cases of common cutaneous eruptions were precipitated, reproduced or exacerbated by Salk poliomyelitis vaccine. These included urticarial, eczematous and psoriasiform eruptions. It is admitted that the incidence of cutaneous eruptions in children and adults vaccinated with

the Salk vaccine is extremely low. Much of the discussion revolved around the possibility that penicillin in the regular Salk vaccine may be the causative agent.

Vitamin K.—In response to a query regarding anaphylactic reaction after an intramuscular injection of vitamin K, the consultant[173] stated that there is no record of anaphylactic shock after the intramuscular injection of vitamin K. This probably represents a rare reaction.

STEROID HORMONES

While it is known that the topical application of hydrocortisone is helpful in some pruritic dermatologic disorders, the mechanism of this effect has not been explained. Some believe that the effects of topical hydrocortisone in reducing itching are secondary to the anti-inflammatory action of the drug. Robin and Kepecs[211] investigated the question of whether or not the antipruritic effect of topical hydrocortisone could be dependent on any measurable alteration of peripheral skin sensation. It was found that the topical application of hydrocortisone has no effect on the sensations in normal skin elicited by cotton stroking. Topical hydrocortisone applied about two hours prior to the production of the histamine wheal has no constant effect upon (a) spontaneous itch, (b) the size of the histamine wheal and (c) itchy skin. Itchy skin responses vary from person to person and appear to be related to certain personality characteristics of the subjects. Frank[85] recorded his attempt to evaluate the antipruritic effect of topical steroids both clinically and experimentally. This was done by removing the stratum corneum by the strip method with cellophane tape. Following this, a drop of 1 :1000 histamine phosphate was applied topically. This consistently produced an erythema, wheal and flare. These areas were then treated with various topical steroids. Hydrocortisone and hydrocortisone diethylaminoacetate were found to have an antipruritic effect when applied two hours prior to histamine on "stripped" skin. When the histamine was applied before the topical steroids, the latter did not shorten the duration of pruritus on "stripped" skin. Clinically hydrocortisone and hydrocortisone diethylaminoacetate, in concentrations of 0.25 per cent, were found to be effective antipruritics in pruritic dermatoses.

In response to a question of absorption of topical steroids to exacerbate or activate a gastric ulcer, it is stated[198] that hydrocortisone is definitely absorbed. Systemic effects may be produced. The risk of the aggravation or possibly the actual production of peptic ulcer should be considered.

Fox and others[84] studied some of the steroids and various other drugs possessing specific pharmacologic properties for their ability to inhibit anaphylaxis in mice. The animals were sensitized by the intraperitoneal injection of large doses of horse serum and were then given the steroids intramuscularly and the other drugs intraperitoneally three to seventy-two hours prior to the administration of a challenging dose of horse serum. Adrenolytic, hypertensive and vasoconstrictive drugs, together with tranquilizers, antihistamines, diuretics, and anti-inflammatory agents, were tested. The degree of protection provided by the medications was determined by a comparison of the survival rate of treated, sensitized mice with the incidence of fatal anaphylaxis in untreated sensitized animals. Chlorpromazine, promazine, reserpine, lysergic acid diethylamide, prednisolone, prednisone, fluorohydrocortisone, and cortisone all gave excellent protection for periods varying from five to forty-eight hours. Meprobamate, sedatives,

antihistamines, anti-inflammatory agents, diuretics, and such steroids as 2 dimethyl-hydrocortone and desoxycorticosterone acetate (DOCA) afforded no protection. The vasoactive agents, including epinephrine, also failed to provide protection. There appears to be some correlation between the chemical structure of the steroids and their ability to protect the sensitized animal. The degree of protection afforded by the steroids was inversely proportional to the degree of sensitivity achieved in the injected mice. As the degree of sensitization increased, larger doses of drugs were required for protection. When the fatality rate in unprotected animals approached 100 per cent, few of the animals were protected by the drugs. In contrast to this, some tranquilizing drugs provided a high degree of protection at levels of maximum sensitization. Sensitized guinea pigs were protected against anaphylaxis by certain tranquilizers but not by the ones that afforded protection to mice. This is probably the result of different pharmacologic properties possessed by the latter drugs and the variation in the type of noxious agents released in the anaphylactic reactions in the two species. In 1951 it was reported that ACTH and cortisone protected a certain percentage of guinea pigs from immediate fatal reversed anaphylaxis but gave little protection against active anaphylaxis. In active anaphylaxis, the shocking reaction is produced by injection of the antigen, while in reversed anaphylaxis antibodies are injected. These antibodies apparently react with antigenic material which is normally present in certain cells and tissues of the animal. Johnstone and Howland[117] wished to repeat some of this work. They studied the effect, in addition, of whole body irradiation on reversed anaphylaxis in normal guinea pigs. It was concluded that cortisone and ACTH protect guinea pigs from immediate fatal reversed anaphylaxis, depending on the dose and time of administration of the hormones. Cortisone and ACTH failed to protect rats. Whole body irradiation did not significantly alter the shock rate in either species. Following whole body irradiation, cortisone failed to protect against fatal reversed anaphylaxis in both species. ACTH did protect guinea pigs but failed to protect rats seven days after irradiation. Irradiation may depress spontaneous adrenal response to stress. It may cause damage to adrenal glandular cells, as was suggested by Edelmann (1951). The doses of cortisone used in this study far exceed any comparable dose per unit of body weight normally used in human beings. The protective effects of ACTH on irradiated guinea pigs may possibly be explained if one assumes that ACTH overcomes the depressive effect of irradiation on the spontaneous adrenal response to stress. It is also possible that the protective adrenal steroid produced in the guinea pig in response to ACTH injections differs in specificity or potency from cortisone given parenterally.

Putkonen and others[168] noted that corticotropin secretion and adrenocortical function are reduced during the prolonged administration of cortisone in patients with certain skin diseases. Studies were made in three men with chronic generalized exfoliative dermatitis. Cortisone therapy had been given for eleven to twenty-seven months and was abruptly discontinued. During the period of hydrocortisone therapy the urinary excretion of 17-ketosteroids was low in all three patients. Immediately after the suspension of treatment, the excretion of 17-ketosteroids increased gradually, but later it declined again. The most rapid and greatest increase was observed in the patient with the lowest maintenance dose of corticotropin. Further observations point to a functional insufficiency of both the testes and the hypophysis in patients on long-continued steroid therapy. Noah and Brand[155] studied the effect of corticosteroid administration on blood

histamine content. Since in the past the blood histamine level has been thought to vary largely, if not entirely, with the leukocyte count, histamine level fluctuations are compared with changes in the total leukocyte count and in constituent cell types. Most of the patients studied were asthmatics. Eleven patients were studied and most pronounced changes in leukocytes and in blood histamine content occurred in those patients given moderate amounts of prednisone. Fluctuations in blood histamine content parallel more closely the fluctuations in basophil values than fluctuations in other cell types. The histamine content of leukocytes varies in different individuals. In one case, neutrophils increased from 53 to 80 per cent in the first three hours without change in the whole blood histamine. Twenty-four hours after prednisone was started, the patient's blood contained almost twice as many neutrophils as originally, but with a decrease of 43 per cent in the original blood histamine value. It is believed that neutrophils contain insignificant quantities of histamine, calculated to amount to an average value of only 3 micrograms of histamine per 10^9 cells.

It is generally known that one of the effects of cortisone derivatives is to inhibit vasodilation on capillaries. Wells[256] showed that various applications containing hydrocortisone could suppress erythema. Results were about the same with ointments containing 0.5 to 2.5 per cent hydrocortisone, but 0.1 per cent fluorohydrocortisone ointment produced a more complete suppression of erythema than 1 per cent hydrocortisone. On a number of occasions it has been reported that fluorohydrocortisone preparations may be absorbed from the skin surface in sufficient amounts to produce systemic effects. Dostrovsky and Cohen[62] studied the effects of hydrocortisone acetate, cortisone, ACTH and hyaluronidase on the leishmanin test in fourteen individuals suffering from Leishmaniasis recidivans. Inhibition of the tuberculin reaction by local injection of compound F acetate has been shown by Goldman (1952). Using hydrocortisone acetate, Appel and others (1954) later produced partial or total inhibition of the reaction of hypersensitivity to lepromin, tuberculin, Frei and Ducrey antigens. It was shown that the systemic administration of cortisone and ACTH partially suppressed the delayed reaction to leishmanin. Intracutaneous injection of hydrocortisone together with the leishmania vaccine caused total inhibition. When the leishmanin test was fully developed, its natural course was shortened and suppressed by the intracutaneous injection of hydrocortisone.

Bukantz and Aubuchon[33] have reviewed the varied and severe complications that occur after the prolonged use of steroids. They record their experience with the use of prednisone and prednisolone in the treatment of a series of thirty-nine children and 113 adults for seasonal and perennial allergies, atopic dermatitis, and other hypersensitive states. While most of the complications referable to hormone excess, growth arrest, diabetes, osteoporosis, psychosis, and so forth are well known, the authors have elaborated on the infection-promoting and anti-inflammatory effects of the steroids. It is necessary to watch carefully those patients who have tuberculosis or histoplasmosis and are also in need of steroid therapy. While these two disorders can be somewhat controlled, viral infections complicating other diseases treated with steroids may be a very serious problem indeed. Chickenpox occurring in a child with atopic dermatitis who is receiving steroid therapy may result in a fatal outcome, and a number of papers recording this eventuality have been published. Management of perforation or hemorrhage of gastrointestinal ulcers is also considered in this interesting paper. Of further interest is the development of peri-

arteritis in arthritic patients who have received steroids over a long period of time. The steroid drugs may be judiciously employed with safety even in long-term management of allergic disease, provided the patients are kept under close surveillance and that the mechanisms of the complications are constantly kept in mind by the physician employing the steroids. Gregoire and Rose[99] found that prednisone and prednisolone were three to five times as effective as cortisone and were free of electrolytic effects in the management of patients with asthma, hay fever, atopic dermatitis, urticaria, polyarteritis nodosa, and disseminated lupus erythematosus. The addition of an antihistamine did not seem to increase the value of the steroid. Brown and Seideman[27] studied the effect of prednisone and prednisolone in a series of thirty-eight patients with allergic dermatoses. Initial dosage was found to be 30 to 40 mg per day for three or four days and a maintenance dose was established at 2.5 mg a day. In cases of atopic dermatitis, for example, it was found that control of the dermatitis with steroids would allow further investigation on an allergic basis. Hyposensitization to various environmental allergens as well as bacterial desensitization could be carried out. Most of the patients in this group received short courses of steroids. Of 190 patients with one of the four major allergic syndromes (bronchial asthma, allergic dermatoses, seasonal allergic rhinitis, or perennial allergic rhinitis), thirty-three developed a total of sixty-seven side reactions. It was necessary to stop steroid therapy in only one instance. Brown and Seideman[28] compared the effectiveness of Ataraxoid (prednisolone-hydroxyzine combination) with prednisolone and hydroxyzine (Atarax) in patients with a number of allergic disorders. Eleven patients had urticaria, six patients had contact dermatitis, and ten had neurodermatitis. By grouping all the allergic patients so treated (total 289, to include other allergic disorders), 75.6 per cent gave an excellent response to the prednisolone-hydroxyzine combination; 48.3 excellent to prednisolone; 32.1 excellent to hydroxyzine; and 24.1 excellent to placebo medication. Side reactions varied from 15 to 37 per cent and were highest with the prednisolone-hydroxyzine combination and with prednisolone alone.

Klingenfuss[126] reviewed the literature on the use of cortisone and corticotropin in the treatment of infants with eczema, emphasizing the origin of this approach by American authors in 1951. He used steroids in a series of thirty children ranging from three months to three years of age with seborrheic dermatitis, infantile eczema and neurodermatitis. Two children with Kaposi's varicelliform eruption were mentioned, but cortisone was ineffective in both of these patients. The daily dose of cortisone was 20, 40 or 80 mg by mouth depending on the severity of the lesions. Duration of treatment was five to forty-eight days. No side effects were noted. There was rapid improvement in the cutaneous lesions. The best results are achieved in infantile eczema when cortisone therapy is combined with the customary treatment—diet, ointments and baths. Mild involvement of the skin is best managed with topical steroid ointment only. The Medical Research Council of Great Britain (Pickering and others[162]) reported the management of periarteritis nodosa in seventeen patients treated with cortisone. Nineteen patients were used as controls. The severity of the constitutional illness appeared to be similar in the two groups. The initial effects of cortisone therapy were dramatic, but a complete suppression of the outward manifestations could be maintained only in three of the fifteen survivors six months after treatment with cortisone was started. Side effects were troublesome. One year after biopsy, seven of the nineteen untreated patients were still alive, as compared with fourteen

of the seventeen treated patients. The interval from biopsy to death ranged from one week to seven months in the untreated patients and from one to eleven months in the treated patients. Final conclusions about the effect of cortisone on life expectancy in patients with polyarteritis nodosa cannot be made, although treatment with cortisone may prolong life according to the results of this study. Chakravarty[39] noted that allergic reactions to streptomycin may develop in 10 per cent of patients who receive this preparation for prolonged periods in the management of tuberculosis. An intradermal test was made with 10 mg of streptomycin in 0.1 ml of sodium chloride solution. One hundred and fifty patients were so tested and clinical indications of allergy were noted in twelve. The test produces a delayed reaction which becomes positive in twelve to twenty-four hours. A method of desensitization to streptomycin is described. Prednisone in 50 mg doses is given orally for one week. After this, along with the 50 mg of prednisone daily, streptomycin is started by intramuscular injection in a dosage of 10 mg and doubled daily until a dose of 800 mg is reached. Following this, 1 gm of streptomycin is given twice a week for four weeks and after this period the prednisone therapy is tapered off and stopped in about two weeks.

A preliminary report on triamcinolone diacetate and its use in the treatment of atopic dermatitis, exfoliative dermatitis, and other diseases was recorded by Rein and others.[206] The majority of patients in their series of twenty-six patients with dermatologic disorders had atopic dermatitis. Sixteen patients with generalized incapacitating atopic dermatitis showed decided improvement. The loading dose was 20 mg of Aristocort with 10 or 12 mg daily recommended for maintenance. In one case, severe generalized angioedema was completely under control in forty-eight hours with 32 mg of Aristocort daily. The incidence of side effects was low. Rein and others were impressed with the greater effectiveness of this preparation over prednisolone. The reviewer has been able to corroborate these data in a series of thirty patients who have generalized atopic dermatitis, exfoliative dermatitis, or lymphomatous erythroderma. In these three conditions, itching is the predominant incapacitating symptom. While the article by Rein mentions weight loss, it could not be determined whether this was the result of decreased appetite of patients or of fluid loss. It could be determined in a number of our patients who had 2 to 3 plus inflammatory edema of the lower extremities that the weight loss was associated with disappearance of pitting edema of the lower extremities. In fact, triamcinolone (Aristocort or Kenacort) should be used in these situations when inflammatory edema of the lower extremities persists even after the use of other steroids. The reviewer is further impressed with the rapid action of this compound. Percentage rates of side effects in clinical use await further and more prolonged study. Loss of body mass and weakness have already been described after the use of triamcinolone. Medrol was used by Feinberg and others[74] in a study of fifty-six patients with asthma, hay fever and dermatitis for periods of one to twenty-two weeks. Methylprednisolone (Medrol) is about equally as effective as prednisone. Medrol, however, has less tendency to stimulate excessive appetite and appeared to cause loss of fluids accumulated from treatment with other steroids. Lackenbacher[127] had significant success in the management of pruritic dermatoses with chlorpheniramine maleate (Chlor-Trimeton maleate). Accordingly it was felt that better results would be obtained with a combination of this antihistamine with 2.5 mg of prednisone (Meticorten) and 75 mg of ascorbic acid. Of thirty patients with contact dermatitis,

eighteen had excellent, nine good, and two moderate effects, while one showed no change whatsoever. Most patients received four tablets of Metreton daily, while 6 per cent of the patients in this series required six tablets daily to obtain a beneficial degree of improvement.

Desai[59] stated that prednisolone was found to be effective as an anti-inflammatory agent in most patients with moderately severe eczema. Initial doses of 15 to 20 mg per day were used. The maintenance dose was 5 to 10 mg per day. A number of side reactions were noted and severe fulminating infections ending in death occurred in two patients who had been given long-continued steroid therapy. Welsh and Ede[258] studied a group of patients with atopic dermatitis, contact dermatitis and other itching eruptions of the skin. These patients were treated with a combination of tar and hydrocortisone ointment which is available as Tarcortin. Twenty-eight of twenty-nine patients with atopic dermatitis were improved 75 to 100 per cent. Results were less striking in patients with contact dermatitis. It was the opinion that the synergistic tar-steroid combination was more effective than either the alcoholic extract of crude coal tar in cream form or hydrocortisone alone.

In discussing steroid therapy in allergic disorders, Kern[123] stated "The more powerful a remedy, the greater is its potential for harmful as well as helpful effects. These effects, both good and bad, will eventually define the limitations of the remedy, and the indications and contraindications for its use." Kern stated that with the use of steroid therapy in allergic disorders, abuses of these agents have also appeared. The adrenal cortex produces at least twenty-eight steroid substances, some of which are: desoxycorticosterone (DOC) which is concerned with salt and water balance; estrogen, androgen and progesterone which affect gonad function; hydrocortisone and aldosterone which influence carbohydrate and protein metabolism, and various enzyme systems. Excess function of the cortex (hypercorticism) results in Cushing's syndrome, while destruction of the adrenals causes Addison's disease. The normal basic replacement need of ACTH is estimated to be three-quarters to one unit per day. For hydrocortisone, the daily quota ranges from 12.5 to 25 mg. When a patient is given a small amount of a hormone, his own gland will produce that much less in order to maintain a normal state. If medication is prolonged, atrophy of disuse of the gland will result. If a patient receives more than one unit of ACTH per day for three months, the anterior lobe will become atrophied, and during this time the excessive stimulus will result in hypertrophy of the adrenals so that after three months they may be three or four times the normal size. If hydrocortisone is given in a daily dose of 12 mg or more, the anterior pituitary does not produce any more ACTH and aften ten days begins to atrophy. At the same time, the adrenal cortex ceases to function and after three months has atrophied to a third or a quarter of its original size. If medication is discontinued, it takes six months for these glands to approach the previous level of physiologic function. When patients have been given steroid therapy for two or three years, there is an extreme degree of adrenal atrophy and iatrogenic Addison's disease is prevalent. The most dramatic results of steroid therapy have been attained with the treatment of severe allergic reactions to known and avoidable allergens. These include exfoliative dermatitis from a drug previously administered, severe reactions to penicillin and other drugs, serum sickness, severe ivy poisoning, trichonosis, Loeffler's syndrome but not tropical eosinophilia, the asthmatic patient who has to undergo emergency operation or bronchography but is sensitive to the contrast

medium, and status asthmaticus when all other measures have been tried and have failed. Steroids should never be used in the treatment of infections for which no antibiotic is available, such as poliomyelitis, tuberculosis, leprosy or brucellosis. Three deaths have been reported in children taking steroids; chickenpox developed and ran a fulminating course. Psychotic patients should never be given steroid therapy. Diabetics will need more insulin while taking steroids. ACTH is a good antigen, and some sensitivity on second administration after a few weeks' interval has been noted. The usual complications after steroid therapy of long duration are noted. In severe generalized eczema, the use of steroids may be necessary. Steroids are indicated in berylliosis and severe purpura and temporarily in polyarteritis nodosa. Attention is called to the mortality statistics in the United States which show a sharp upswing in deaths from asthma in those over age fifty since the introduction of the steroids, and probably as a result of their use. Bookman[22] reviewed some of the complications of steroid therapy in the management of allergic disease. Patients with allergic eczema may be treated with excellent results using time-honored methods without resorting to steroids. Steroids apparently have no appreciable effect on the antigen-antibody level of activity. Anaphylactic shock does not appear to be influenced by the steroids. Circulating antibodies and circulating reagins apparently show no fundamental change as a result of these drugs. It has also been observed that the steroids neither intensify nor diminish reactions to the allergic skin test. In eczema, short courses of corticosteroids can be used in preference to local applications in those patients who suffer acute exacerbations or fail to respond to milder forms of treatment. Steroid ointments have not been uniformly effective enough to justify their expense to the patient when considerable areas of skin are involved.

Allanby[2] reported that between 1949 and 1956, 400 patients were treated with steroids at Guy's Hospital. Eighteen of these patients died either while receiving the preparations or soon after therapy was discontinued. It was thought that steroid therapy was responsible for nine deaths. Seven of the eighteen patients died from infection and four patients died of massive hemorrhage, usually from the gastrointestinal tract. One asthmatic patient died apparently from pulmonary embolism shortly after cessation of corticotropin therapy. A patient suffering from ankylosing spondylitis was thought to have died from hypersensitivity to corticotropin given intravenously. A case was recorded of a fifty-nine-year-old man who was started with 25 units of ACTH in glucose by intravenous infusion; after two days the spondylitis showed remarkable improvement. While the infusion was being given, he complained of dyspnea and a slight fever developed. The dyspnea became more severe during the next two infusions. When the infusion was discontinued, his symptoms subsided almost immediately. Severe dyspnea on the sixth day terminated the infusion and although the joint condition improved, he died twelve hours after the last infusion. Autopsy showed a small amount of free fluid in each pleural cavity, and a considerable amount of thick, tenacious sputum in the trachea and bronchi.

This reviewer adds one further case of hypersensitivity to ACTH. A forty-two-year-old woman was seen with generalized nummular eczema which had resisted most forms of therapy in the hands of excellent dermatologists. Following appropriate studies, it was decided to give her a series of intravenous ACTH infusions, and one containing 20 mg of ACTH in 5 per cent glucose solution was started. No prior medication

had been given. Within three to four minutes after the start of the infusion, the patient complained of tickling sensations in the throat and general prickly sensations over the trunk and extremities. This was followed in a few minutes by generalized urticaria and localized angioedema of the eyes and lips. All this was observed by a technician who was making patch tests on a patient in a neighboring bed and, being familiar with allergic disorders, she immediately stopped the infusion and notified me of the situation. The patient responded rapidly to epinephrine. The company supplying this particular brand of ACTH supplied us with vials of antigen containing beef, pork and lamb. Skin tests were made about ten days after this occurrence but the results were negative. Passive transfer studies also gave negative results. Plumer and Armstrong[165] presented the histories of three patients which illustrate that the corticosteroids may cause death from adrenocortical failure. One patient who had been treated with 50 mg of cortisone daily for seven months for severe rheumatoid arthritis died shortly after an arthroplasty; autopsy revealed atrophy of the adrenal cortex. The pathologist ascribed the death to acute adrenal insufficiency. Low adrenocortical function may be present for many months after the cessation of corticosteroid therapy. In the two remaining patients who were given cortisone therapy, mild infection was followed by coma, hyperthermia and death.

In response to a query on steroid-induced hemorrhage, the consultant[187] stated that a hemorrhagic tendency may follow the administration of either adrenocorticoid hormones or salicylates. Large doses of salicylates may result in varying degrees of hypoprothrombinemia, with a resultant hemorrhagic tendency. A single dose of corticotropin (ACTH) or the adrenocorticoid hormones may prolong the clotting time appreciably within a few hours and result in a hemorrhagic tendency. A thromboembolic phenomenon, on the other hand, as well as thrombosis of various blood vessels, has also been observed in patients following long-term adrenal hormone therapy. The skin, lungs, coronary vessels, brain, and deep and superficial vessels of the legs, as well as other vascular areas, have reportedly been involved in hemorrhage or thrombosis after hormone therapy. The incidence of these complications apparently is not great. In sixteen of fifty-four patients given steroid hormones for periods varying from several days to several years, Carone and Liebon,[36] of the Yale University School of Medicine, discovered postmortem evidence of acute pancreatitis or peripancreatic fat necrosis or both. Steroid hormones (however improved!) should be used in minimal doses in short courses and only when the indications are absolute.[65] They are not, and never have been, substitutes for established methods used by a well-trained conscientious allergist.

Stefanini in 1956 reported ecchymoses following prednisone therapy and at that time stated that ascorbic acid deficiency accounted for this finding. He[238] has administered 100 mg of ascorbic acid twice daily to patients who are treated with corticotropin or steroid hormones over a period longer than two weeks. Osteoporosis is sometimes seen in patients with pemphigus and other disorders receiving long-term corticosteroid therapy. Treatment of the osseous demineralization is difficult.[197] Testosterone can be administered by injection or by buccal tablets. Doses of 300 mg of testosterone cyclopentylpropionate every second and third week may be used. Estrogens may be given in addition. Large doses of calcium, phosphorus and vitamin D should be administered orally. Orthopedic appliances will often re-

lieve symptoms of osteoporosis. In spite of these measures, osteoporosis may persist or even progress.

Most patients with eczematous dermatitis respond in a satisfactory manner to topical application of hydrocortisone ointments. If response is poor, most dermatologists will switch from one type of steroid to another. Sams and Smith[222] reported contact dermatitis caused by hydrocortisone ointment in a patient who was found to be sensitive to the emulsifying agents in a hydrophilic ointment base. The combination of sodium lauryl sulfate and wax in petrolatum showed an erythematous papular response by patch test.

MISCELLANEOUS ALLERGIES AND BRIEF REVIEWS

Various phases and mechanisms of immunologic tissue injury were discussed by Weiser.[254] Antigens and antibodies probably get into cells because of surface membrane activity, allowing invaginations of these membranes to occur. These invaginations frequently pinch off inside the cell to form vesicles. Actually the vesicles may be carried to the opposite side of the cell and evaginated in the same manner. Work with fluorescent antibody suggests that injected foreign antigens actually invade cells all over the body, even the cell nuclei, in a matter of minutes. The localization of antigens in cells is extremely important, since the cells and tissue sites at which antigens become fixed and persist may determine in great measure the subsequent allergic responses and the sites of lesions. By fluorescent antibody technique it can be shown that gamma globulin is present in large amounts in the lesions of rheumatic fever, glomerulonephritis and polyarteritis nodosa. Little is known, however, about the cellular localization of the P-K or reagin type of antibody. With respect to the cellular sites at which antigen and antibody unite, one can visualize that they may unite at the surface of the cell, within the cell or both. Complement also plays a role in some of these reactions. It is certain that complement levels frequently drop during allergic episodes, but we know very little concerning the exact role that complement may play in such reactions. Mediators of one sort or another also take part in immunologic tissue injury. Evidence has shown that histamine is not the only mediator agent in anaphylaxis. Papaverine will protect against anaphylaxis in the guinea pig, but not against histamine shock. When lung tissue of a sensitized guinea pig and the uterus of a rat in the same bath are exposed to antigen, the lung tissue of the guinea pig contracts and so does the uterus of the rat. Apparently some mediator which was given off by the sensitized lung of the guinea pig caused the contraction of the nonsensitized uterus of the rat. Since we know that the rat uterus is not sensitive to histamine, some other mediator must have been involved. It has been known for some time that egg-white injury in the rat results from the destruction of mast cells in the feet and in the snouts of these animals by the action of ovomucoid. Mast cells are very abundant in these locations and the destruction of large numbers by the ovomucoid results in the local liberation of considerable quantities of histamine and serotonin. It was shown that serotonin, and not histamine, was largely responsible for the local tissue injury. This major action of serotonin may be peculiar to the rat, as it is highly resistant to histamine and highly sensitive to serotonin. The mast cell has many activities. Increasing evidence has indicated that it functions as a unicellular endocrine and is engaged in the production as well as the liberation of heparin, histamine and possibly serotonin and hyaluronic acid. Mast cell distribution in the various species is a very

interesting subject. In man, the uterus, thymus, bladder, tongue, skin large and small vessels and intestine all have abundant numbers of mast cells. Moderate amounts are found in the medium sized vessels, testes, heart, pancreas, spleen and salivary glands. Sparse amounts are found in the liver, kidney, lung, adrenal glands, hypophysis and placenta. The mast cell is apparently one of the most easily injured cells in the body. In the case of the skin it has been shown that mere stroking will cause injury to these cells. Study of the mast cells may provide an answer to many unexplained phenomena in hypersensitivity reactions.

Cases of zirconium deodorant granulomas were abstracted in Dermatologic Allergy for last year. Rubin et al,[219] Pinkus and Botvinick,[164] and Sheard et al[230] have described patients in whom a granulomatous axillary reaction developed after the use of deodorant sticks that were found to contain zirconium compound. It remained for Shelley and Hurley[231] to study and describe the allergic origin of zirconium deodorant granulomas. The relationship of various granulomas as seen in man is described. The various diseases in which a granulomatous response is present number almost fifty, ranging from allergic granulomatosis and blastomycosis to Whipple's disease and xanthomatosis. On the basis of both experimental and clinical studies, it was shown that these deodorant granulomas result from a specific acquired allergic hypersensitivity to zirconium. Thirty healthy adult male subjects vigorously rubbed a standard commercial zirconium stick deodorant in the left axilla every morning for five minutes. The right axilla served as a control for the effect of zirconium. After a month, a chronic noninflammatory eruption of the left axilla developed in one patient. Two weeks later, some of the papules were excised and histologic study revealed an early epithelioid granuloma. Further studies with shaving likewise produced granulomas in the sensitized experimental group. Further experiments with the introduction of extremely small amounts of zirconium produced a form of epithelioid granuloma. It was assumed that lepra bacillus extract and sarcoid tissue, used in the Mitsuda and Kveim test respectively, contain highly specific allergens in trace amounts. The allergic state now encompasses part of the granulomatous reactions in the body and appropriate intracutaneous tests must be undertaken in studying the nature of any granuloma. Unbelievably small amounts of zirconium may produce a granuloma. As little as 0.2 mircograms of sodium zirconium lactate was capable of producing a small but grossly visible skin lesion in one of the highly sensitized patients. From this work and its theoretical extension, it is conceivable that "zirconiosis" of the lungs could ensue in industrial workers following inhalation of zirconium dusts. Physicians who deal with individuals working with zirconium must be alert to the possbility of such a new entity. No cross-sensitization phenomena have been observed with the zirconium ion as yet.

Among the many hypotheses offered to explain the mechanism of inflammation and histamine release is the concept set forth by Ungar (1953) that the activation of plasma (fibrinolysin) by inflammatory stimuli can account for the phenomena of inflammation and the release of histamine in all cases. If this hypothesis is valid, it might be assumed that the fluid which accumulates in wheals induced by allergens would have fibrinolytic activity. Rebell and others[202] studied this problem by testing fluid from wheals induced by the intradermal injection of histamine, compound 48-80 a histaminic releaser, giant ragweed, Alternaria, western ragweed and house dust for fibrinolytic activity by a modified fibrin plate method. No marked fibrinolytic activity was observed, al-

though the addition of streptolysin to the fluid revealed a plasminogen content comparable to that of serum. The data tend to minimize, but do not rule out, the possible role of plasmin in the intracutaneous response to inhalant allergens.

Considerable evidence has accumulated in the past ten years to support the hypothesis that plasma cells or lymphocytes are a major source of antibody production. Urbach and Koenigstein, in 1924, were the first to develop a method for the passive transfer of tissue antibodies. Landsteiner and Chase published their observations on the transfer of delayed type sensitivity in animals. In human beings, delayed type sensitivity to tuberculin and to bacterial antigens has been successfully transferred by means of suspensions of viable leukocytes, disrupted leukocytes and leukocytic extracts. The work of Chase is quoted to indicate that immediate type sensitivity has been successfully transferred by viable cells in animals. This was done by using as donors guinea pigs highly sensitive to picryl chloride. When large quantities of splenic or lymph node cells were transferred to nonsensitive recipient animals, both a specific cutaneous sensitivity of the delayed type and circulating anaphylactic antibodies developed. Leukocytic transfer from human donors to human recipients of immediate type sensitivity to ragweed pollen and timothy grass pollen by means of leukocytic extracts has also been reported. A repetition of this work by Freedman and others[86] showed that the delayed type skin sensitivity to tuberculin was transferred to tuberculin-negative human recipients by means of leukocytic extracts and disrupted leukocytes obtained from the peripheral blood of tuberculin-sensitive human donors. Attempts to transfer immediate type skin sensitivity to ragweed pollen, penicillin and horse serum from human donors to human recipients by means of leukocytic extracts or disrupted leukocytes were unsuccessful. In a like manner, viable leukocytes did not transfer sensitivity.

Previous reports demonstrate a striking regional variation in skin histamine levels in the guinea pig. Thus, it occurred to Johnson[115] that a similar variation might occur in humans. Studies revealed that the histamine levels vary decidedly in different skin regions of human beings, with a higher histamine content on the upper lip and eyelid and decreasing amounts in the submental triangle, scalp, infraclavicular region, lower part of the abdomen and the skin over the xiphoid cartilage. It is most interesting that the mouse, rat and cat—animals with the highest skin histamine levels—are most refractory to all types of cutaneous allergic responses. The guinea pig, rabbit and man, with relatively low skin histamine levels, are skin-reactive animals. West and Parratt[259] discussed their findings with 5-hydroxytryptamine (5-HT). This is an amine related to, and probably derived from, the amino acid tryptophan. It is the authors' belief that this agent in addition to histamine should be considered as part of the system concerned with the reaction of the skin to injury and the subsequent formation of edema. While present elsewhere, 5-HT has recently been associated with tissue mast cells in the skin of the rat. Such cells in the skin of many species, including man, are rich in histamine and it is obviously important to study the occurrence, distribution and reactivity of both amines in the skin. Moreover, no single substance has yet been found to account for the hyperemia and increased vascular permeability associated with many common reactions to injury.

While the role of histamine appears important in some reactions, much evidence indicates that it is not the sole active agent. Experiments with edema-producing substances in the rat indicate that 5-HT as well as hista-

mine may be responsible for the vasodilatation and increased permeability which lead to edema. 5-HT is present in wasp venom and is also present with histamine and acetylcholine in the sting of the nettle. When a guinea pig is sensitized to horse serum and its uterine horn treated with antigen, maximal contraction occurs after the first addition of the specific antigen (Schultz-Dale reaction). If the uterine horn is tested in the presence of an antihistamine the reaction is blocked, whereas the presence of a 5-hydroxytryptamine antagonist, such as "BOL 148," the bromo derivative of lysergic acid diethylamide, does not affect the reaction. The Schultz-Dale reaction in the guinea pig is, therefore, caused by the formation of histamine. Similar experiments with rat uteri produce a completely different result. Histamine has no effect, whereas "BOL 148" completely blocks the reaction showing (according to Sanyal and West[223]) that in the rat 5-hydroxyptamine is produced by the antigen-antibody reaction.

In a previous study, Cormia and others had shown that localized itching was produced regularly by the intradermal injection of streptokinase, profibrinolysin, fibrinolysin and epidermal protease. Itching could also be produced by endopeptidases, such as trypsin, ficin and papain, which are found in plants and animals.[49] In some normal individuals, the intradermal injection of these agents was followed by scattered itching lasting for one to eight hours. Further studies of the proteolytic activity in the blood of normal patients and in those with severe pruritus did not reveal any particular alteration of activity. Hahn and others[101] studied the alteration of plasma electrophoretic patterns and anaphylactic reactions in protein-depleted dogs. Electrophoretic studies were carried out before and after the depletion period. The total plasma proteins showed an average reduction of about 20 per cent. The A/G ratio, however, decreased approximately 85 per cent. The albumin varied from 40 to 50 per cent under normal conditions and was reduced to 9 to 13 per cent in the depleted state. The total alpha-globulins were increased in each protein-depleted animal, as were the beta-1 and beta-2 globulins. The values for gamma globulin were approximately doubled in the depleted state. If the anaphylactic-antibody-containing globulin fraction was decreased in the depleted animals, this could not be detected in the above studies. Depleted animals exhibited milder anaphylactic manifestations or none at all, and none died. All eleven control animals exhibited the usual symptoms of anaphylaxis, with the exception of one which manifested excessive itching only. Two of these dogs died within twelve hours.

It has been found that parenteral administration of penicillinase inactivated all circulating penicillin, both in guinea pigs and in human beings. The therapeutic use of purified penicillinase for inactivation of circulating penicillin in patients suffering allergic reactions to penicillin was suggested. Sensitization of rabbits with penicillinase was reported earlier and Fisher, Cooke and others[79] made studies in guinea pigs and rabbits on experimental sensitization with penicillinase. Thirty-six guinea pigs and nine rabbits were given five semiweekly injections of penicillinase. Some animals received pure penicillinase, whereas others received a combination of this agent plus human albumin or Freund's adjuvant or both. All of the animals became sensitive to penicillinase. This was demonstrated by the immediate response to skin tests with penicillinase and the finding of Arthus response in some animals as well as precipitins and agglutinins.

Considerable evidence has indicated that delayed hypersensitivity reactions to bacterial, viral and fungal agents are diminished in patients with the lymphoma-leukemia complex. This group includes patients with

Hodgkin's disease, lymphosarcoma, leukemia, multiple myeloma, mycosis fungoides, and so forth. Epstein[71] determined that twenty-seven patients with the lymphoma-leukemia complex showed a pronounced decrease in capacity to react to contact allergens, 2, 4-dinitro-chlorobenzene and para-nitrosodimethyl aniline. This corresponds to the decreased sensitivity to other delayed type allergens. These patients were all ambulatory out-patients who were not acutely ill at the time of testing. Adequate controls were used.

Patch tests have been widely employed to demonstrate cutaneous sensitivity to eczematous contact type dermatitis. Various modifications of the standard patch test technique have been proposed. One such proposal involved the use of increased pressure by inserting a block of sponge plastic between the impermeable material of the routine patch and the covering adhesive tape. With this technique it was possible to elicit a positive reaction when the routine patch test gave a negative result (Fernström, 1955). With this in mind, Anderson and others[4] tested the influence of varying physical factors on patch test responses. Wooden squares or disks with sharp edges were used and wooden squares or disks with rounded edges were also employed. In addition, rubber squares of various thicknesses were used between the patch test material and the covering adhesive tape. It was concluded that in carrying out patch tests with solid materials, pressure upon a hard substance can produce a false reaction. This is almost invariably marginal at the site of an edge. The reaction under certain conditions can be diffuse, however, covering the entire patch test area. Sponge rubber of less than 0.5 mm thickness will not produce this nonspecific marginal effect. Pressure can potentiate a patch test with an allergen, particularly at higher dilutions or in instances of a low degree of sensitivity. In discussing this paper, Sulzberger[242] stated that in reading tests for many years, the edge effect had been previously noted—even when the material used in testing was not hard and abrasive or damaging to the skin any more than a soft piece of cotton. It is believed that this occurs because of increased concentration of allergen at the edge of the testing square. This can be demonstrated by simply putting a dilute solution of dye on a cotton square and watching it diffuse out to the periphery. Sulzberger felt that while this particular study had great merit, it would not be wise to use different concentrations and other variations of the patch tests so long as it took years to establish certain standards and criteria for existing routine patch testing.

Paraphenylenediamine is a frequent and potent sensitizer, producing many cases of allergic, eczematous, contact type dermatitis. At the Skin and Cancer Unit of the New York University Hospital, Fisher and others[78] reported a series of 712 patients who were subjected to patch tests in 1956; twenty-six or 3.6 per cent, gave strongly positive reactions to this agent. The persistence of allergic eczematous sensitivity was demonstrated by retention of sensitivity in forty-six of fifty patients over a period of three to ten years. Cross-sensitivity was demonstrated with paraphenylenediamine in eleven patients who gave cross reactions to benzocaine, four who gave cross reactions to procaine and benzocaine, three who reacted to PABA and benzocaine and one who reacted to sulfanilamide. Repeated exposure to paraphenylenediamine did not affect the level of this sensitivity. Repeated exposure to paraphenylenediamine or related allergens did not, as a rule, broaden the established spectrum of cross sensitivity of patients studied in this series.

R. L. Mayer[141] noted in discussion that the existence of various patterns

within a specific type of cross sensitization probably results from the fact that sensitization is not caused by the original substance, but by various breakdown products when the antigen is metabolized.

Winkelmann[262] reviewed our knowledge of the clinical and pathologic findings in the skin in cases of anaphylactoid pupura. This is known by a number of names which include: purpura rheumatica, Schönlein-Henoch syndrome, allergic angiitis, allergic vasculitis, and so forth. Related entities include allergic granulomatosis, Wegener's granulomatosis and systemic periarteritis nodosa. Cutaneous signs have remarkable symmetry and always eventuate into some type of purpura. History of drug sensitivity is often obtained. Platelet count, bleeding and clotting times are universally normal. The pathologic findings include hemorrhage secondary to an intense vasculitis. Local necrosis of vessel walls is diagnostic. A series of five cases is presented to show the relationship of the cutaneous changes to those in other organs. Rest, supportive measures, and at times steroids are recommended. Sneddon[236] reported that most dermatologic purpuras belong to the category in which an increase in permeability or fragility of the capillary wall is noted. Purpura resulting from drugs may be caused by: (1) damage to platelet formation in the bone marrow producing true thrombocytopenic purpura; (2) production of the circulating antibody which, in the presence of the drug and complement, results in lysis of the platelets and damages the capillaries, and (3) true vascular damage without evidence of effect on blood elements. Canizares[35] stated that purpura is occasionally associated with itching, and several cases have been reported elsewhere. Several cases have been reported in Argentina and an abstract was published in the *A.M.A. Archives of Dermatology*, June 1956. These cases were not associated with cirrhosis of the liver. In further discussion,[160] Peck stated that there is a whole group of purpuras that are definitely on an allergic basis, produced by foods and other proved factors. Associated itching is characteristic of many of these allergic purpuras. Dysproteinemic purpura is described by Hambrick.[103] This is a more or less chronic condition characterized by purpura and by a serum protein pattern which is abnormal qualitatively, quantitatively, or both. Three types of this condition have been recognized. In 1943, "purpura hyperglobulinemica" was described by Waldenström. His patients had chronic, recurrent purpura of the legs. This was accompanied by an increase in serum gamma globulin and elevated sedimentation rate without the presence of definite, recognizable systemic disease. Subsequently, macroglobulinemia of Waldenström in 1944 and cryoglobulinemia of Lerner and Watson in 1947 were recognized as distinct dysproteinemic syndromes with hyperglobulinemia. The main features of the Waldenström type consist of a recurrent purpuric eruption appearing primarily on the legs; an increase in the total serum globulin, reflecting a great increase in gamma globulin; an increased sedimentation rate secondary to hyperglobulinemia; a normochromic anemia, and a benign course without the presence of recognizable, underlying disease. The condition may be secondary to an underlying disease such as sarcoidosis or lupus erythematosus, cirrhosis of the liver, arthritis, and so forth. Others are primary or idiopathic. The macroglobulinemica of Waldenström is a chronic syndrome characterized by lassitude, dyspnea, mucous membrane bleeding, mild lymphadenopathy, diffuse osteoporosis and hepatosplenomegaly occurring in elderly men, accompanied by macroglobulins in the serum. Only one patient had purpura in seventeen cases recorded. The Sia water test is usually positive. Cryoglobulins have been present in some cases. The

term cryoglobulinemia was introduced by Lerner and Watson to describe cold-precipitable serum globulins. Cryoglobulins have been demonstrated in many diseases, mainly in multiple myeloma and also in rheumatoid arthritis, lupus erythematosus, lymphomas, hepatic cirrhosis, scleroderma, and others. Clinically, purpura is present as well as bleeding from the nose and mouth, retinal hemorrhages, vascular phenomena including Raynaud's gangrene, and multiple arterial and venous occlusions. Purpura usually follows exposure to cold and occurs chiefly on the extremities and head. Cold urticaria may precede purpura. Hambrick added a further case of purpura hyperglobulinemica of Waldenström to the series.

Symon and others[244] discussed observations on hyperglobulinemic purpura. This syndrome has been observed most often in middle-aged women who demonstrate showers of petechiae which may occur on all parts of the body but are most numerous on the lower extremities. An abnormality of the capillary wall is present. Generalized lymphadenopathy is usual, and hepatosplenomegaly may occur. The course is usually benign. Electrophoretic analysis of the serum showed an increased globulin protein in the gamma fraction. No cryoglobulins were detected. Hemorrhagic disturbances may be classified in four groups on the basis of their presumptive pathogenic mechanism: (1) those caused by a primary defect of the vascular wall; (2) those resulting from a qualitative or quantitative platelet deficiency; (3) those caused by abnormalities in the blood coagulation factors, and (4) those resulting from qualitative or quantitative disturbances of the blood proteins (dysproteinemias). Waldenström described a new syndrome—"purpura hyperglobulinemica"; this is characterized by relapsing purpura of the lower extremities, persistent increase of the serum globulin fraction, mild normochromic anemia, leukemia, elevated erythrosedimentation rate and increased total serum proteins between 8.7 and 9.8 gm per 100 cc. Following electrophoretic studies it was concluded that the hyperglobulinemia was caused by an increase of gamma globulin; the albumin fraction was not decreased and the electrophoretic pattern was of the "virus" type as seen in lymphogranuloma venereum. The cryoglobulins were not demonstrable. Fleischmajer and others[80] presented the case of a thirty-four-year-old married woman first examined in 1955 with a history of recurrent episodes of purpura of four years' duration, involving the lower extremities. This patient showed further classical evidence of the disorder described by Waldenström. The pathogenesis of purpura of idiopathic hyperglobulinemia remains obscure. The possibility of invasion of the vascular wall by the increased globulins with resultant capillary fragility is presented. Some feel that the alteration of the small vessels is based on an allergic mechanism. In discussion, Rostenberg[214] also felt that an allergic mechanism was possible. In further discussion, Baer[7] stated that dermatologists have become increasingly interested in purpuric eruptions on the lower extremities. A number of cases of cryoglobulinemic purpura have been reported by dermatologists. A less commonly known syndrome is the autoerythrocyte sensitization in women, which produces painful bruising.

Cerutti and Santojanni[38] discussed their findings in cases of polyarteritis nodosa. Histologically, vascular changes are of primary importance and show the characteristics of serous inflammation and fibrinoid degeneration which occur mainly in the media and adventitia. Changes in the intima of smallest arterioles and capillaries have also been observed, and even veins may be involved. In reporting eight cases, the polymorphous nature of the skin lesions is emphasized. While nodular lesions are common, infiltrative,

plaquelike lesions with marked hemorrhagic character are also seen. In one case the condition resembled panniculitis, and diffuse vasculitis of the granulomatous type was present at the dermal-hypodermal border. The toxic-infectious and allergic-infectious origin of some of the cases are recorded. Steroids are successful in some cases.

The management of progressive, systemic scleroderma continues to present a serious problem. Casten and Boucek[37] reported their experience with the use of relaxin—an extract from the ovaries of pregnant sows—in twenty-three patients with scleroderma. These patients were treated from six to thirty months and significant decrease in skin tightness, Raynaud's phenomenon and trophic ulceration was observed. No toxic or undesirable side effects have been observed in this series. The reviewer notes, however, that two anaphylactoid reactions have been observed at the Lahey Clinic in the last twelve months in patients with scleroderma. It should be noted that relaxin is derived from the ovaries of pregnant sows and may be given intramuscularly or intravenously. Hence, switching the route of administration or allowing for a period of sensitization may be followed by allergic reactions. One of our patients died within minutes of an intravenous injection and postmortem examination showed no evidence of disease to account for the sudden death. The usual findings of systemic scleroderma were recorded. Berk[17] followed the course of a patient with disseminated lupus erythematosus for nine years. Episodes of allergy, such as urticaria, dermographism and sensitivity to sulfonamides antedated the onset of the disease. Seasonal episodes occurred upon long exposure to sunlight. Allergic reactions to gold, phenylbutazone, and Benemid appeared. The author believes that the progressive insults to the body by repeated hypersensitivity reactions precipitated clinical disseminated lupus erythematosus. Huntley and Dees[118] described five young patients who showed a combination of chronic eczema, thrombocytopenic purpura and chronic suppurative otitis media. The outcome was fatal in all five cases. Three of the patients had a family history of both allergy and purpura. Milk allergy was suspected. All suffered repeated infections. Four had eosinophilia ranging from 14 to 45 per cent. Four died at approximately two years of age but one lived until seven and one-half years of age. The cause of death in all cases was infection. Four patients who had undergone splenectomy died within a few months after the operation.

Lamb and others[128] discussed the most common type of polymorphic light eruption which is a plaquelike eruption showing slight follicular plugging. This condition clears without atrophy in the winter, affects the posterior cheek and mastoid areas primarily and is seen mostly in men (90 per cent). This eruption must be differentiated from discoid lupus erythematosus. The papular and prurigo-like type of polymorphic light eruption may resemble eczematous contact dermatitis. The erythema multiforme type of solar dermatitis may be unilateral and a distribution may appear on the left cheek owing to exposure from the driver's seat of motor vehicles. Chloroquine and quinacrine are satisfactory in the treatment of mild cases. Men are given 500 I.U. of chorionic gonadotropic hormone daily or every other day for prolonged periods. Older men receive 50 mg of testosterone weekly plus A-Fil creme. Women receive 25 to 50 mg of testosterone weekly with 0.25 gm of chloroquine twice daily. In by far the greater percentage of previously reported cases of solar erythema in which light tests have been elicited, the action spectrum was below 3900 A. Lamb and others[129] have observed patients who showed severe erythema perstans

after exposure to fluorescent lighting. Others who are sensitive to blue light in cases of polymorphic light eruptions do not seem to improve with the use of the antimalarial drugs. The method of generation of fluorescent light is described. Patients who gave positive reactions to tests with fluorescent lights are described. Therapy in three cases consisted of removal of the source of light and the parenteral use of testosterone propionate. Levy and others[131] reported some unusual reactions in ultraviolet light test sites. These reactions occurred in four of twenty-seven patients with polymorphous light eruption who were tested with hot quartz ultraviolet light. In one case, erythema persisted in the test sites for seven months after a single exposure. Chloroquine administration had no effect on the reaction of the test sites. In two cases, papules appeared in previously tested sites even though they were not re-exposed directly to sunlight. Typical polymorphous light eruption followed in areas exposed to sunlight. These unusual papular reactions suggested that polymorphous light eruption is a true photoallergic disease and it is also suggested that these reactions are strongly reminiscent of a similar phenomenon seen in cases of allergic eczematous contact dermatitis. A query is made with reference to a fifty-one-year-old woman in whom an urticarial eruption with edema and marked pruritus developed after exposure to the sun. The answer[194] states that this is clearly an instance of hypersensitivity to light and that the range of the ultraviolet spectrum to which different individuals are sensitive differs. This could be determined by a special apparatus with differential light filters. From the clinical standpoint, however, this is not necessary. The tolerance of the patient to light can be increased by repeated daily doses with gradually increasing exposure, and for temporary effect one could use antihistamines or creams containing sun screens such as para-aminobenzoic acid. The reviewer notes that no reference is made to the chloroquine class of compounds which are usually so effective in light sensitivity.

Foubert and Stier[83] studied the problem of antigenic relationships in Hymenoptera. The species used in this work were wasps, hornets, yellow jackets and honeybees. Gel diffusion studies suggest that the yellow jacket, yellow hornet, black hornet, wasp, and honeybee contain common antigens. In addition, each insect contains several antigens specific for the individual genus. The antigens varied in their ability to sensitize. The most potent sensitizer was yellow jacket antigen, while black hornet antigen was the least potent. If the stinging insect can be identified, desensitization may proceed with a single insect extract. Desensitization with a combined antigen would seem advisable in most cases, however, and these extracts should contain a mixture of at least bee, wasp, yellow jacket and hornet extracts. Morris[150] reported that insect bites are nearly as prevalent in office workers as they are among workers in industrial plants. In this situation the experienced exterminator can manage the problem almost as well as the dermatologist. Fleas brought into the office by workers who have pets at home as well as the parasites which may be present on the office cat may be responsible. Fleas are attracted to white stockings and their presence may soon be confirmed by this technique. Bedbugs, human or animal scabies and head lice may attack office personnel especially in offices where many girls work together. Fowl mites (poultry and pigeons), rat mites and food mites (causing cheese itch, fig itch, copra itch, barley itch, cottonseed itch) may also be incriminated. One exterminator reports that a common cause of dermatitis in office workers is the handling of frayed old manila folders! These are made by the kraft process and contain cellulose,

casein glues or rosin as well as various fillers and coated with formaldehyde or melanine formaldehyde resins.

In reply to the question of recurrent painful aphthae in a twenty-six-year-old woman, one consultant[172] stated that the etiology of recurrent and painful aphthae is unknown. Although the herpes virus could not be demonstrated by several groups of investigators, good therapeutic results have been reported following repeated smallpox vaccinations. Elimination diets may be effective. Injections of snake venom and immunization with herpine vaccine have been of value in some patients, while diluted Fowler's solution as a mouth wash and histamine desensitization have given good results in others with this condition. The second consultant felt that the answer in this case may be concerned with nutritional and deficiency disease. Trial with therapeutic doses of nicotinic acid, riboflavin, and large doses of vitamin A should be instituted. Local treatment with diluted hydrogen peroxide and a very mild alkaline mouth wash are suggested. Sircus and others[235] have made an extensive study of recurrent aphthous ulceration of the mouth. One in five members of the population suffers at one time or another from recurrent aphthous ulcerations of the mouth. An outstanding feature, indicated by 21 per cent of the patients, was a period of mental stress prior to the onset of aphthae. The etiology of this disorder remains obscure and in their study most methods of treatment resulted in failure. Relief was obtained by aureomycin in some cases, and an occasional spectacular result was seen as the result of suggestion alone. Zwerling[271] studied an unselected group of 200 patients with aphthous stomatitis. A mouth rinse or gargle containing Chlorpactin was used for ten-minute periods every three hours. This preparation consists of modified hypochlorous acid derivatives. Over 90 per cent of the patients showed decided improvement within eight hours. The preparation is said to have viricidal effects and for lesions of the larynx, Chlorpactin WCS-90 is recommended. Chlorpactin WCS-60 was used for mouth lesions.

Some forms of recurrent herpes simplex result from trigger factors which may include foods and drugs. Adoni and Tschan[1] have observed that poliomyelitis vaccine was effective in controlling recurrent herpes simplex in a twenty-year-old man with a history of this disorder since childhood. Two standard dose injections of poliomyelitis were administered during the summer of 1956 and to this date the fever blisters have not recurred. An additional case report of a twenty-five-year-old man with a similar complaint is described. This patient is a laboratory technician dealing with transferring tissue cultures containing the HeLa cell which was impregnated with all three types of poliomyelitis virus. From time to time the patient accidentally ingested and swallowed part of the liquid cultures. Since his accidental ingestions of the poliomyelitis virus, he has had no recurrent episodes of herpes simplex.

It is probably well known by this time that otitis externa does not depend primarily on the bacterial flora which is found at the time of activity. Feinmesser and others[75] studied the bacterial and mycotic flora of the external ear in fifty-five cases of otitis externa as well as of the healthy ear in thirty-seven cases of unilateral otitis externa. Fifteen healthy control subjects were also used. Staphylococcus albus, either alone or in association with diphtheroids and various fungi, was found in the ears of all healthy control subjects. Rubin[218] studied a large series of patients with otitis externa and found pathogenic staphylococci and Pseudomonas aeruginosa. The impression was that P. aeruginosa flourishes much more freely in the hot climates than in the colder ones. The pH of the cutaneous

surface of the external auditory canal was below 7 in more than 30 per cent of the cases. The reviewer notes that in most inflammatory skin conditions, the pH of the skin is on the alkaline side; thus, the normal acid mantle of the skin is impaired.

Friedman and others[87] described an instance of severe asthmatic reaction following the subcutaneous administration of typhoid-paratyphoid vaccine. The patient was a thirteen-year-old boy with a past history of bronchial asthma and ragweed hay fever; he had received the usual immunizing injections against pertussis, tetanus and diphtheria. In 1952 he had been given a series of three subcutaneous injections of typhoid vaccine. In 1953 and 1954, booster doses of triple typhoid vaccine were administered without untoward effects. In June 1955 another booster dose of 0.5 ml of typhoid vaccine was given subcutaneously. Within ten minutes a severe asthmatic attack occurred although the patient had been free of asthma for over a year. Epinephrine gave immediate relief. This reaction was traced, after extensive skin testing, to filtration of biologicals through silk. Cross neutralization tests showed that the silk-filtered vaccines exhausted all the silk antibodies in the patient's serum, whereas those vaccines that were not silk-filtered did not affect the reactivity of the serum. The silk antigen in biological products is a potential hazard to any silk-sensitive individual. Brown and Coleman[29] described three patients in whom severe immediate allergic reactions developed after the injection of certain immunizing agents. These included diphtheria and tetanus toxoids and pertussis vaccine combined (triple antigen), tetanus toxoid, and human gamma globulin. It could be determined that these reactions were caused by the silk used in the technical process of filtering some of these biologic agents. The reviewer notes that many patients with atopic dermatitis show large intradermal reactions to silk antigen. It would be of interest to recall from old records whether or not these patients showed any peculiar skin reactions after the administration of childhood immunizing mixtures. Certain companies are now replacing silk filters with other types. Coleman[41] likewise has studied the problem of the silk antigen as a contaminant in biological agents. He recorded five cases from the literature and has personal knowledge of five additional unreported cases of this type of allergic accident. In 250 consecutive atopic patients tested intracutaneously with silk extract, positive reactions occurred in sixty-nine, an incidence of approximately 27 per cent. At least nine of the ten patients who experienced allergic reactions to silk as a contaminant were atopic. This parallels the incidence of atopy in "anaphylactic" reactors to penicillin.

Two patients with congenital agammaglobulinemia were described by Porter.[166] It should be remembered that patients with this disorder show repeated bacterial infection starting in early childhood, and have serum gamma globulin levels below 30 mg per 100 ml in the presence of normal total serum proteins. They have an inability to produce circulating antibodies. There is an absence of plasma cells from the bone marrow and isohemagglutinins from the blood. Protection against infection may be obtained by injection of gamma globulin. The delayed type of hypersensitivity was normally produced in response to antigens. Circulating antibodies were not present in the gamma globulin fraction of the serum, however. The tuberculin response is apparently independent of the serum gamma globulin. Parrot and Laborde[159] stated that *in vitro* studies showed that normal human serum is capable of fixing a part of the histamine that is added to it. This histaminopexic power, which can be measured and expressed in terms of percentage, is said to be lacking in the serum of

patients with allergic manifestations such as asthma, urticaria and eczema. The effect of a subcutaneous injection of normal human serum on patients with allergic manifestations, including four with eczema, was noted. Relief of a temporary type was noted in the majority of patients, but recurrences were also reported. Hampton[104] discussed fundamental research in allergy as it applies to antigen-antibody reactions and methods of preventing antibody formation. Research in histamine metabolism, enzymes and autosensitization, as well as collagen disease, is brought up to date as of 1956. This is a basic article with an excellent bibliography. The relationship of some skin diseases to bacterial, pollen and food sensitization was discussed by Andrews and Domonkos.[5] Follow-up studies have been carried out for twenty years or more in some patients with pustular bacterid, and in some of these cases the relationship to focal infection seems well established. Twelve patients with pustular bacterid were promptly and unquestionably cured permanently of recalcitrant pustular eruptions limited to the palms and soles by the removal of focal infections. An additional three patients in this group were cured by antibiotics given orally, hydrocortisone or antibiotic local remedies. The principles used by these outstanding dermatologists in the management of infantile eczema and eczema in adults are recorded. However, it is the opinion that in generalized neurodermatitis with an atopic history, skin testing is of little value; it is recognized moreover that the methods of testing are extremely crude and that manifold ingredients in clothing, cosmetics and environment may play an undiscovered role. It is difficult to distinguish clinically, for example, sensitivity to feather or mold inhalant allergy from contact dermatitis caused by nail polish, hair lacquer and similar contactants in patients who have periorbital dermatitis. Skin manifestations of inhalant allergens such as feathers, pollens and molds, are described.

Collins-Williams and Ratner[47] have again done a thoroughgoing work in their current review of pediatric allergy. The section on atopic dermatitis and steroids in atopic dermatitis, as well as the review of urticaria and angioedema in children, has largely been covered in previous reviews of progress in dermatologic allergy over the past three years (1954-1957). Nevertheless, additional references have been included and this section may be read again with profit. Several reports of eczema vaccinatum and Kaposi's varicelliform eruption are included. One author finds that vaccinia-immune gamma globulin is very effective in the treatment of eczema vaccinatum. The administration of this substance concurrently with the vaccine would be useful in persons with eczema who must be vaccinated for exposure to infection. If vaccinia-immune gamma globulin is not available, ordinary gamma globulin is worth while but is a great deal less effective. The reviewer had an opportunity to use immune gamma globulin from donors previously vaccinated, with good effect—at least temporarily—in a critically ill thirty-year-old man with Kaposi's varicelliform eruption.

A query is raised with reference to a fifty-one-year-old woman in whom severe pain across the diaphragm, abdominal distention and anuria developed, associated with edema of the face, lips and sometimes in the mouth. This occurs after the ingestion of spirits. The consultant[186] stated that allergy to alcohol *per se* is quite rare; more likely is the possibility of sensitivity to a protein moiety contained in spirituous beverages. The second consultant stated that the edema associated with marked fluid retention with oliguria and termination in polyuria suggests sensitization. Treatment suggested was conventional—including a careful history, avoidance of alcohol, skin test inquiry and symptomatic management.

The question of ethylene disulfonate as a treatment for allergic disorders comes up from time to time. In response to a query, the consultant[184] stated that there have been favorable reports of its use in children with eczema but these reports are uncritical and the studies were never adequately controlled. Archibald (1945) came to the conclusion that any effect the product had was the same as that of distilled water. Pertinent literature on this subject was reviewed by the Council on Pharmacy and Chemistry in *The Journal of the American Medical Association,* August 31, 1946, and during the past ten to twelve years there has been no additional evidence to support the value of ethylene disulfonate.

Erythema neonatorum allergicum is a dermatitis of the newborn infant; it consists of erythema, papules, and pustules appearing in the first three days of life and disappearing by the sixth day. About 10 per cent of the cases are severe enough to result in the development of pustules. These are sterile and contain over 90 per cent eosinophils. It is important to differentiate this eruption from potentially serious cutaneous disorders affecting the infant. Taylor and Bondurant[247] studied the occurrence rate of this condition in 200 newborn infants. Erythema neonatorum allergicum must be differentiated from pyoderma, exanthems, miliaria, diaper rashes, and physiologic postnatal redness. Of 200 consecutive newborn infants observed, 31 per cent had erythema neonatorum allergicum during their hospital stay. The etiology is unknown, but some investigators believe that allergy may play a role. O'Connor[158] reported two fatal cases of erythema multiforme exudativum; detailed postmortem findings are recorded. The diagnosis of the first patient recorded was Stevens-Johnson syndrome —severe and probably caused by drug reaction to phenolphthalein. The cause of death in the second patient was not established, except for the clinical diagnosis. The literature on the Stevens-Johnson syndrome is reviewed. It is suggested that because of the same basic pattern in variations of the disease, an all-inclusive term—"the ocular-mucocutaneous syndrome"—might be preferable. The case of a fifty-three-year-old woman who had a mottled purpuric eruption of the legs with recurrent ulcers of the left ankle area was presented by Nelson.[152] It was thought that the ulcers were associated with cryoglobulins. Symptomatic cryoglobulinemia may occur with such diseases as multiple myeloma, lymphoma, periarteritis nodosa, and cirrhosis of the liver. In contrast, cases of essential cryoglobulinemia have been reported, in which no underlying disease can be identified. Either type of patient may show edema of the feet, livedo reticularis, superficial ulcers, purpura, bleeding from the mucous membranes, a positive Rumpel-Leede test, various manifestations of sensitivity to cold and, ultimately, gangrene of the digits associated with Raynaud's phenomena. Nelson and Schwimmer[153] discussed the results of the Kveim test in 335 persons during the past seven years. The reaction was positive in 74 per cent of seventy-two patients with biopsy-confirmed sarcoidosis. Of fifty-six tested during the active phase of the illness, all but three showed positive results. It was felt that the Kveim reaction is highly specific for sarcoidosis and that it is infrequently positive in other diseases.

A query was made in reference to a sixty-five-year-old Chinese man who had a twenty-five-year history of intolerable itching of the face. The results of physical and laboratory examinations were negative except for hypertension of ten years' duration. Treatment had been unsuccessful. The first consultant[178] stated that systemic diseases—especially endocrine, nephritic, and hepatic disorders—must be ruled out. The twenty-five-year duration would seem to eliminate visceral, malignant or lymphoblastic dis-

eases. Toxic allergic reactions to foods or drugs, especially narcotics, must be considered, as must psychogenic and environmental factors. The second consultant likewise requested a search for underlying systemic diseases such as leukemia, scleroderma, lupus erythematosus, and Hodgkin's disease. In addition, however, he felt that the patient should have an intensive allergic survey. In the reviewer's opinion, itching of this type is almost always psychogenic. Dameshek[170] stated that the symptom of itching after a shower should be regarded as a clue toward the diagnosis of polycythemia vera. Severe itching after a shower or tub bath occurs in at least half the patients with polycythemia vera. This symptom is often so severe that the patient dreads taking baths and may even give them up altogether.

LeVan[130] studied the effect of anxiety and emotional stress in patients with atopic dermatitis, neurodermatitis, urticaria, pruritus ani et vulvae, and other inflammatory dermatoses of the skin. It was felt that the tranquilizing drugs were far less likely to produce the side reactions associated with barbiturates, chloral hydrate, bromides and antihistamine drugs. Four classes of tranquilizers were studied: Rauwolfia alkaloids (Reserpine), phenothiazines (chlorpromazine), propanedial dicarbamate (meprobamate), and diphenylmethanes (hydroxyzine). Chlorpromazine and Reserpine were used four times daily in a group of 274 patients. Sixty per cent showed a slight to pronounced beneficial effect. Unpleasant side reactions limited the usefulness of these drugs. Two hundred and twenty-four patients with various allergic skin disorders were given Equanil and forty-one patients were given hydroxyzine hydrochloride (Atarax). Based upon consistency of response, it is believed that meprobamate and hydroxyzine are preferable to the Rauwolfia and chlorpromazine drugs. It is important to continue therapy for at least two weeks before discarding a drug as not being beneficial in a particular case.

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TRUTH

"My main interest, almost the only one, is the love of truth, whether pleasant or not, whether useful or not. Truth is self-sufficient, and there is nothing to which it can be subordinated without loss."—GEORGE SARTON, 1884-1956.

Papers of Interest

Granirer, L. W.: Exfoliative dermatitis as a complication of chloroquine (aralen) therapy in rheumatoid arthritis. A.M.A. Arch. Dermat., 77:722 (June) 1958.
Onset of symptoms occurred twenty days after initiation of therapy with a single dose of 250 mg chloroquine daily in a patient in whom there was no previous history of dermatitis, allergy, or drug sensitivity.

Gerhart, W. F., Van Ommen, R. A., McCormack, L. J., and Brown, C. H.: Chlorpromazine jaundice. Clinical course, hepatic-function tests, and pathologic findings-summary of twenty cases. A.M.A. Arch. Int. Med., 101:1085 (June) 1958.
A "hepatitis regimen" (high-carbohydrate high-protein diet, bed rest and supplemental vitamins) should be instituted. In five patients, steroids were ineffective.

Favorite, F. G.: The imported fire ant. Pub. Health Rep., 73:445 (May) 1958.
Recommended treatment for anaphylactoid-type reactions is parenteral Benadryl® or epinephrine.

Kory, R. C., Pribek, R. A., and Sternlieb, R. O.: Comparative evaluation of epinephrine and aminophylline as bronchodilator agents. Am. Rev. Tuberc., 77:729 (May) 1958.
Epinephrine injected subcutaneously was better than aminophylline given intravenously.

Trethewie, E. R.: The effect of butazolidine on the anaphylactic lung. Australian J. Exper. Biol. & M. Sc., 35:541 (Dec.) 1957.
Butazolidine inhibits the release of both histamine and Slow Reacting Substances from the perfused anaphylactic lung of the guinea pig. In a concentration of 2.5-5 mg/100 ml it had no effect on the sensitivity of the guinea pig intestine to histamine.

Adamkiewicz, V. W., and Langlois, Y. L.: Insulin, mast cell components, and "anaphylactoid" inflammation. Canad. J. Biochem. & Physiol., 36:483 (May) 1958.
Antihistaminic agents inhibit "anaphylactoid reactions" in rats. The inhibatory effect is not reversible by histamine, heparin or serotonin.

Matsaniotis, N., Jacobs, J., and Smith, M. H. D.: Hypersensitivity reactions associated with sodium para-aminosalicylate therapy. Pediatrics, 21:781 (May) 1958.
Three of 100 tuberculous children developed sensitivity and were successfully desensitized.

Zilberg, B.: Anuria following penicillin administration. South African M. J., 32:350 (Mar. 29) 1958.
Anuria appears to have been a manifestation of sensitivity in a male infant.

Storstein, O., Helle, I., and Rokseth, R.: The effect of theophylline ethylenediamine on the pulmonary circulation. Am. Heart J., 55:781 (May) 1958.
Dilating effect on the arterioles of the systemic and pulmonary circulations lessens cardiac burden.

Suhrland, L. G., Arquilla, E. R., and Weisberger, A. S.: The effect of prednisolone on circulating antibody formation in animals immunized with human platelet antigen. J. Lab. & Clin. Med., 51:724 (May) 1958.
In the rabbit, formation of circulating antibodies to human platelets is inhibited.

Germuth, F. G., Jr., and Pollack, A. D.: The production of lesions of "serum sickness" in normal animals by the passive transfer of antibody in the presence of antigen. Bull. Johns Hopkins Hosp., 102:245 (May) 1958.
Serum sickness reproduced by passive transfer of antibody.

Raffel, S.: Immunologic disease. Pediatrics, 21:849 (May) 1958.
Detailed, masterful discussion of protean manifestations of hypersensitivity and of antibodies. Read and re-read.

Schwartz, M. J., and Norton, W. S.: Thrombocytopenia and leukopenia associated with use of sulfamethoxypyridazine. (Kynex, Midicel). J.A.M.A., 167:457 (May 24) 1958.
One case of thrombocytopenia and another of thrombocytopenia and leukopenia.

Zetzel, L., and Kaplan, H.: Liver damage concurrent with iproniazid administration. New England J. Med., 258:1209 (June 12) 1958.
Three cases of severe liver disorder improved during treatment with iproniazid. The relation between the liver disease and iproniazid administration is discussed theoretically and clinically.

Anderson, P. C., and Fleck, R. L.: Drug eruption due to fumagillin complicated by trichophytosis. A.M.A. Arch. Dermat., 77:720 (June) 1958.
Two different skin responses; a wide-spread maculapapular eruption and also a marked scaling process of the hands and feet. Two cases of the scaling reaction were associated with Trichophyton rubrum infections which responded to antifungal treatment.

Smarr, E. R., Wolf, H., and Pressman, M. D.: Experiences with marsilid with report of one death. Am. J. Psychiat., 114:1115 (June) 1958.
Marsilid although markedly effective for treatment of ambulatory depressions is toxic to a dangerous degree to some patients and to mild degrees in others.

Haizlip, T. M., and Ewing, J. A.: Meprobamate habituation. A controlled clinical study. New England J. Med., 258:1181 (June 12) 1958.
Objective evidence of abstinence was noted in forty-four of forty-seven patients. Meprobamate should be discontinued slowly to obviate withdrawal symptoms.

Winkelmann, R. K.: Clinical and pathologic findings in the skin in anaphylactoid purpura (allergic angiitis). Proc. Staff Meet. Mayo Clin., 33:277 (May 28) 1958.
Five cases of a clinical form of purpura associated with acute necrosis or chronic granulomatous vasculitis of the walls of cutaneous blood vessels. Bleeding affecting any organ system may occur.

Smith, R.: Therapy of common skin eruptions. Ontario Med. Rev., 25:572 (June) 1958.
A summary.

Abernathy, R. S., Strem, E. L., and Good, R. A.: Chronic asthma in childhood: double-blind controlled study of treatment with gamma-globulin. Pediatrics, 21:980 (June) 1958.
In twenty-two children there was no difference in the incidence of infection between treatment groups and the controls.

Sidi, E., Hincky, M., and Longueville, R.: Cross-sensitization between neomycin and streptomycin. J. Invest. Dermat., 30:225 (May) 1958.
Patients sensitive to either are sensitive to both.

Novak, A. F., Fieger, E. A., and Bailey, M. E.: Chlortetracycline for preserving gulf oysters. Food Tech., 12:237 (May) 1958.
Recommended amount is 20 ppm. Additional oysters must be added to chicken, fish, and milk as possible source of antibiotic ingestion or contact.

Wells, F. E., Fry, J. L., Marion, W. W., and Stadelman, W. J.: Relative efficacy of three tetracyclines with poultry meat. Food Tech., 11:656 (Dec.) 1957.
Chlortetracycline best for prolonging storage time as compared to oxytetracycline or tetracycline.

Munroe, D. S.: Hypersensitivity to penicillin. Canad. M.A.J., 78:924 (June 15) 1958.
Review of types and predictability of reactions, and uses of penicillinase.

Hilleman, M. R., Flatley, F. J., Anderson, S. A., Lueking, M. L., and Levinson, D. J.: Antibody response in volunteers to adenovirus vaccine and correlation of antibody with immunity. J. Immunol., 80:299 (Apr.) 1958.
Lack of neutralizing antibody leads to susceptibility to infection.

News Items

GERMAN SOCIETY OF ALLERGOLOGY

The Seventh Congress of the German Society of Allergology will be held on October 8-10, 1959, in Bad Lippspringe, West Germany.

The Scientific Program will include the following: Allergy to House Dust and Moulds, and Hyposensitization (Theoretical and Practical Aspects).

INTERNATIONAL SOCIETY OF INTERNAL MEDICINE

The Sixth International Congress for Internal Medicine will be held in Basel (Switzerland) from August 24-27, 1960. This Congress will be organized in conjunction with the Swiss Society for Internal Medicine. For further details, apply to the Secretariat of the Sixth International Congress for Internal Medicine, 13 Steinentorstr., Basel, Switzerland.

AKRON ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

The Akron Academy of Ophthalmology and Otolaryngology announces a Post-Graduate Course in Allergy and the Endocrinological Aspects of Allergy by Herbert J. Rinkel, M.D., Kansas City, Missouri, and Z. Z. Godlowski, M.D., Associate in Medicine at Northwestern University, Chicago, Illinois, to be held on May 4-6, 1959, at the Akron City Club, Ohio Building, Akron, Ohio.

Registration fee is $35.00. A.A.G.P. credit may be given if desired. For further information, contact A. L. Peter, M.D., 656 West Market Street, Akron 3, Ohio.

SOCIETY ELECTIONS

Allergists of San Antonio

The newly elected officers of the Allergists of San Antonio for the year 1959 are: Dr. Boen Swinny, President; Dr. J. W. H. Rouse, Vice President; and Dr. Bernard T. Fein, Secretary-Treasurer.

Los Angeles Society of Allergy

The newly elected officers of the Los Angeles Society of Allergy for the year 1959 are: Dr. Ralph Bookman, President; Dr. Isadore Pitesky, Vice President; and Dr. Catherine G. Pearson, Secretary-Treasurer.

Philadelphia Allergy Society

The newly elected officers of the Philadelphia Allergy Society for the year 1959 are: Dr. Alex Peters, President; Dr. Charles Classen, Vice President; and Dr. Sonia Stupniker, Secretary-Treasurer.

ERRATUM—ACA MEMBERSHIP DIRECTORY

On page 95 of the 1959 Membership Directory of The American College of Allergists, the subtitle "Minnesota" was inadvertently omitted between the last alphabetically listed city of Michigan, namely, Ypsilanti, and the first city to be listed under Minnesota, namely, Hutchinson.

NEWS ITEMS

TWO NEW FOUNDATIONS IN UTRECHT

The Foundation for Experimental Research in Allergology has been founded in Utrecht. The President of the Foundation, Dr. Fr. A. Nelemans, is assisted by Prof. Dr. U. G. Bijlsma. The Foundation welcomes suggestions for subjects on which research should be done. It plans not only to do the investigations, but to issue reports annually and organize courses of lectures.

The Foundation for Research into the Social Consequences of Bronchial Asthma has also been founded under the direction of Prof. Dr. S. J. Groenman, co-operating with the sociologist, Dr. E. Land. This Foundation will investigate the social consequences of bronchial asthma and the social conditions of individual asthmatic patients.

Inquiries should be directed to each Foundation, but may be mediated by Dr. W. J. Quarles van Ufford, Emmalaan 17, Utrecht, Holland.

PEDIATRIC ALLERGY SEMINAR

A Pediatric Allergy Seminar will be presented by the Department of Pediatrics, Allergy Section, University of Tennessee, May 20, 21 and 22, 1959. W. L. Rucks, M.D., will act as co-ordinator.

Wednesday, May 20

A.M.

8:00 Registration
9:00 Welcome—Tom Mitchell, M.D.
9:15 Introduction—W. L. Rucks, M.D.
10:00 Cow's Milk Allergy in Pediatrics—Susan Dees, M.D.
11:00 Food Allergy—Frederic Speer, M.D.
12:00 Pathophysiology of Asthma—(Speaker to be announced)

Luncheon—1:00 P.M.

P.M.

2:00 Complications of Dermal and Respiratory Allergy—Lloyd Crawford, M.D.
3:00 Nasal Allergies—Joseph Haywood, M.D.
4:00 Non-Specific Factors in Asthma—Susan Dees, M.D.

Thursday, May 21

A.M.

9:00 Clinic
11:00 Aerosol, Sputum, and Enzymes in the Asthmatic Child—Don L. Thurston, M.D.
12:00 Dermagraphia—Joseph Haywood, M.D.

Luncheon—1:00 P.M.

P.M.

2:00 Human Milk Versus the Cow in the Feeding of Small Potentially Allergic Premature Infants—David Goltman, M.D.
3:00 Resistant Asthma—Frederic Speer, M.D.
4:00 Eczematoid Dermatitis—Joseph Haywood, M.D.

Friday, May 22

A.M.

9:00 Uncommon Allergic Reactions—Susan Dees, M.D.
10:00 Important Seasonal and Non-Seasonal Inhalants—Frederic Speer, M.D.
11:00 Fluid Therapy in Asthmatics—Don L. Thurston, M.D.

Adjournment—12:00 M.